EXHIBIT 5

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

PACIRA BIOSCIENCES, INC., Plaintiff, v. AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC., et al., Defendants.	Civil Action No. _____ **DECLARATION OF CATHERINE VANDEPITTE, MD**

I, Catherine Vandepitte, MD, PhD, do hereby declare:

1. I am over 18 years of age and have personal knowledge of the information contained herein. I currently reside in Belgium. I have my M.D. from the Katholieke Universiteit Leuven (K.U.L) in Belgium, where I graduated *cum laude* in 2003. I also hold a PhD in Biomedical Sciences form K.U.L., which I earned in 2018. I am currently employed as an attending anesthesiologist at Ziekenhuis Oost-Limburg, a hospital in Genk, Belgium, with a subspecialty in Regional Anesthesia and Acute Pain Management. I also currently serve as a Senior Research Associate at the New York School of Regional Anesthesia in New York, NY. I am not receiving compensation for this declaration.

2. Over the past several years, in collaboration with other clinicians, I have conducted three clinical studies related to liposomal bupivacaine, a slow-release analgesic marketed under the brand name EXPAREL. These studies are:

a. Vandepitte C, et al.: Addition of Liposome Bupivacaine to Bupivacaine Hcl Versus Bupivacaine Hcl Alone for Interscalene Brachial Plexus Block in Patients Having Major Shoulder Surgery. Reg Anesth Pain Med 2017; 42:334–41 [hereinafter, "Shoulder Study"] (attached as **Exhibit A**);

b. Vandepitte C, et al.: Effect of Bupivacaine Liposome Injectable Suspension on Sensory Blockade and Analgesia for Dupuytren Contracture Release. J. of Hand Surgery Global Online 2019; 191-197 [hereinafter, "Hand Study"] (attached as **Exhibit B**); and

c. Van Boxstael S, et al.: Analgesia after Hallux Valgus Osteotomy Posterior Tibial and Deep Peroneal Nerve Ankle Blocks with Bupivacaine Liposome Injectable Suspension+Bupivacaine HCl vs. Bupivacaine HCl vs. General Anesthesia Alone: A Randomized Clinical Trial. Clinical Res Foot Ankle 2019, 7:3 [hereinafter, "Ankle Study"] (attached as **Exhibit C**).

3. Bupivacaine is an analgesic that can be injected directly into a surgical site. Liposomal bupivacaine is a modified form of bupivacaine that uses a liposomal encapsulation to allow bupivacaine to be released over time, with the intent to prolong pain relief and reduce the use of opioids and other pain medications.

4. The February 2021 issue of *Anesthesiology* contained an article by Nasir Hussain, MD, MSc, et. al, titled: "Perineural Liposomal Bupivacaine Is Not Superior to Nonliposomal Bupivacaine for Peripheral Nerve Block Analgesia." I will refer to this article as the "Hussain Article."

5. The Hussain Article purports to conduct a meta-analysis of randomized trials that compared the use of bupivacaine alone to liposomal bupivacaine. Hussain Article at 1 (description of "Methods").

6. However, despite its stated intended methods, the Hussain Article includes only one of my three studies in its analysis, the 2017 Shoulder Study, inexplicably excluding the other two studies, even though these satisfy the Article's eligibility criteria. All three studies found

that liposomal bupivacaine improved patients' pain scores and/or reduced the need for opioids by clinically significant margins.

7. First, the Hand Study considered patients that underwent surgery to address a condition called Dupuytren contracture, a condition in which one or more fingers become permanently bent in a flexed state. We conducted a randomized trial of 32 subjects, which were split into two groups of 16 patients. The first group received bupivacaine alone, while the second group received a mixture of bupivacaine (for an immediate analgesic benefit) and liposomal bupivacaine (for continued release over time). Our study found that that the second group experienced a sensory block nearly four times longer than subjects in the first group. Further, subjects in the second group had improved pain scores on average between 1 to 2 points on a 10-point pain scale, without experiencing increased side-effects or impaired function of the arm or hand after surgery. Exhibit B at 191, 193-95.

8. The Hussain Article asserts (at p. 2) that it searched the U.S. clinical trial registry (http://www.clinicaltrials.gov) for eligible studies, as well as conducting a literature search. However, the Hand Study was included in that registry but was not included in the Hussain Article's meta-analysis.

9. Second, the Ankle Study assessed patients undergoing surgery for bunion repair. This study compared three groups of patients. The first group received only general anesthesia (14 patients); the second group received bupivacaine alone (14 patients); and the third group received a mixture of bupivacaine and liposomal bupivacaine (much like in the Hand Study) (12 patients). The Ankle Study evaluated whether liposomal bupivacaine, when added to a nerve block, reduced patient consumption of opioids. It found that when liposomal bupivacaine was used, it decreased average opioid consumption by a clinically significant amount compared to

bupivacaine alone and to general anesthesia. Patients receiving liposomal bupivacaine mixed with bupivacaine alone had an average consumption of only 9.6 mg of morphine equivalents, compared to 26.8 mg in the bupivacaine alone group, and 60.4 in the general anesthesia group. Exhibit C at 1000291.

10. The Ankle Study was also registered with clinicaltrials.gov but likewise was not included with the Hussain Article. Although the Hussain Article did not consider studies that used general anesthesia as a comparator to liposomal bupivacaine, because the Ankle Study also used bupivacaine alone as a comparator, that brought the study within the eligibility criteria for the Hussain Article. Nonetheless, the Hussain Article did not consider the Ankle Study.

11. Finally, even though the Hussain Article purports to considers the Shoulder Study within its review set, it chooses to exclude it from the Article's final conclusions due to the study's sponsorship by Pacira, the manufacturer of EXPAREL. However, simply because a study is funded by industry does not by itself invalidate the results. A well-designed and executed study still provides relevant data. In fact, in many instances, industry-funded research can result in some of the most valuable data because the research is well-funded. In fact, FDA pharmaceutical approvals are based on research not only funded but actually conducted by the manufacturer of a drug, and the world is currently racing to vaccinate the global population for the COVID-19 virus based on studies by the vaccination manufacturers. To simply dismiss an industry-funded study without articulating any specific concern with respect to the methodology or the analysis, as the Hussain Article did, is arbitrary and risks skewing the results of any meta-analysis by excluding relevant data. The Shoulder Study was conducted with approval by the Ziekenhuis Oost-Limburg (ZOL) Ethics Committee and the Belgian governmental agency

(FAGG). It was peer-reviewed and published in the journal *Regional Anesthesia and Acute Pain Medicine (RAPM)*.

12. The Shoulder Study reviewed 52 adult patients undergoing major shoulder surgery. Similar to the other two studies, we divided the subjects into two groups, one receiving bupivacaine alone and the other receiving a mixture of bupivacaine and liposomal bupivacaine. The Shoulder Study concluded that "Liposome bupivacaine added to standard bupivacaine may lower pain and enhance patient's satisfaction in the first postoperative week even in the setting of multimodal analgesia for major shoulder surgery." Exhibit A at 334. Additionally, in evaluating pain scores for the patients' "worst pain" ratings on a 0-10 scale, those receiving liposomal bupivacaine had an average score of 3.6, compared to 5.3 for those receiving bupivacaine alone. *Id.*

13. The Hussain Article reaches a negative conclusion of liposomal bupivacaine, but entirely fails to consider two of the studies I conducted with positive results and, although it identifies the third study, it arbitrarily dismisses the study's positive conclusion regarding liposomal bupivacaine.

Date: March 30, 2021

Dr. Catherine Vandepitte, MD, PhD

EXHIBIT A

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ORIGINAL ARTICLE

Addition of Liposome Bupivacaine to Bupivacaine HCl Versus Bupivacaine HCl Alone for Interscalene Brachial Plexus Block in Patients Having Major Shoulder Surgery

Catherine Vandepitte, MD, Max Kuroda, PhD, MPH,† Richard Witvrouw, MD,* Ludwig Anne, MD,* Johan Bellemans, MD, PhD,* Kristoff Corten, MD, PhD,* Pascal Vanelderen, MD, PhD,*‡ Dieter Mesotten, MD, PhD,*‡ Ine Leunen, MD,* Micheline Heylen,§ Sam Van Boxstael, MD,* Monika Golebiewski, MD,† Marc Van de Velde, MD, PhD,§ Nebojsa Nick Knezevic, MD, PhD,† and Admir Hadzic, MD, PhD*†§*

Background and Objectives: We examined whether liposome bupivacaine (Exparel) given in the interscalene brachial plexus block lowers pain in the setting of multimodal postoperative pain management for major shoulder surgery.

Methods: Fifty-two adult patients were randomized to receive either 5 mL of 0.25% bupivacaine HCl immediately followed by 10 mL of liposome bupivacaine 133 mg (n 26) or 15 mL of 0.25% standard bupivacaine alone (n 26) in interscalene brachial plexus block. The primary outcome (worst pain in the first postoperative week) was assessed by the Modified Brief Pain Inventory short form. Secondary outcomes were overall satisfaction with analgesia (OBAS), functionality of the surgical arm, sleep duration, time to first opioid (tramadol) request and opioid consumption (mEq), sensory-motor block characteristics, and the occurrence of adverse effects.

Results: Worst pain was lower in patients given liposome bupivacaine added to standard bupivacaine than in patients given standard bupivacaine alone (generalized estimating equation [GEE] estimated marginal mean values, 3.6 ± 0.3 vs 5.3 ± 0.4 points on the Numeric Rating Scale, respectively, although the effect was modest, 1.6 ± 0.5; 95% confidence interval, 0.8 2.5). Total OBAS scores indicated greater satisfaction (GEE estimated marginal mean values, 1.8 ± 0.3 vs 3.3 ± 0.4 on total OBAS, respectively, with modest effect, difference, 1.4 ± 0.5; 95% confidence interval, 0.5 2.4). There were no differences in any of the other secondary outcomes.

Conclusions: Liposome bupivacaine added to standard bupivacaine may lower pain and enhance patient's satisfaction in the first postoperative week even in the setting of multimodal analgesia for major shoulder surgery.

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The study was conducted with Ziekenhuis Öost-Limburg (ZOL) Ethics Committee and Belgian governmental agency (FAGG) approvals for investigational new drugs (EudraCT 2015-001559-55), and was registered with clinicaltrials.gov (NCT02554357) on July 11, 2015.

Dr. Hadzic has consulted and advised for Philipps, GE, Sonosite, Codman & Shrutleff, Inc. (Johnson and Johnson), Cadence, Pacira, Baxter, and B. Braun Medical. His recent industry-sponsored research includes Baxter and Pacira Pharma. Dr. Hadzic receives royalty income from B. Braun Medical.

Funding: This study was funded by Pacira Pharmaceuticals.

The rest of the authors declare no conflict of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.rapm.org).

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This study was registered with clinicaltrials.gov (NCT02554357) on July 11, 2015, by Principal Investigator Catherine Vandepitte, MD.

(*Reg Anesth Pain Med* 2017;42: 334 341)

The interscalene brachial plexus block (ISBPB) is commonly used for shoulder surgery[1]; however, the analgesic benefits of the block are typically limited to less than 24 hours even with long acting local anesthetics, such as bupivacaine and ropivacaine.[2–5] To prolong analgesia postoperatively, a number of different adju vants have been studied, albeit with inconsistent analgesic benefit and relatively short duration.[6–9] Continuous interscalene blocks (catheters) have also been used to prolong postoperative analge sia[10,11]; however, the catheters may dislodge from their therapeu tic position.[12] In addition, placement and daily maintenance of nerve block catheters typically require higher technical skills and are more time consuming to manage than single injection blocks.

Liposome bupivacaine (bupivacaine liposome injectable sus pension, Exparel; Pacira Pharmaceuticals Inc, Parsippany Troy Hills, New Jersey) is a multivesicular formulation of bupivacaine indicated for soft tissue infiltration into the surgical site to produce postsurgical analgesia.[13–15] Liposome bupivacaine is not approved by the United States Food and Drug Administration (FDA) for nerve block infiltration. In a dose response study, administration of lipo some bupivacaine in a femoral nerve block in healthy volunteers resulted in neural blockade more than 24 hours.[16] Subsequently, liposome bupivacaine was found to reduce postoperative pain and opioid use in patients having total knee replacement with an adverse effect profile similar to that of placebo.[17] However, that study was designed to meet the FDA standard for approval of an algesic agents, which rests on the comparison of investigational agents versus placebo. Consequently, the study did not offer in formation on the efficacy of this new formulation in conjunction with existing long acting local anesthetics such as bupivacaine and/or within a clinical setting of multimodal postoperative pain management.

In this study, we tested the ability of liposome bupivacaine to extend the postoperative analgesia of standard bupivacaine in ISBPB for patients having major shoulder surgery in a clinical set ting of multimodal postoperative pain management. Because re cently published pharmacokinetic data indicated delayed onset of bupivacaine release in perineural applications (maximum plasma drug concentration, Cmax, 12 to 36 hours after infiltration),[18] we added liposome bupivacaine to standard bupivacaine and com pared its analgesic effects to that of standard bupivacaine alone. Our primary hypothesis was that the worst pain scores in the first postoperative week are lower in patients given liposome bupivacaine added to standard bupivacaine compared with patients given

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standard bupivacaine alone. Secondarily, we hypothesized that overall satisfaction with pain management is also improved.

METHODS

The study was conducted with Ziekenhuis Öost Limburg (ZOL) Ethics Committee and Belgian governmental agency (FAGG) approvals for investigational new drugs (EudraCT 2015 001559 55), and was registered with clinicaltrials.gov (NCT02554357). Fifty two patients, American Society of Anesthesiologists physical status I to III, 18 years or older who were scheduled for elective major shoulder surgery (rotator cuff repair or total shoulder replacement) were enrolled in this prospective double blinded randomized clini cal study after signing informed consent (Fig. 1). Exclusion criteria included a history of allergy to a local anesthetic, preexisting neu rological deficits, psychiatric or cognitive disorders that could in terfere with perioperative evaluation, recent history (<3 months) of drug or alcohol abuse, concomitant opioid therapy, preexisting coagulation disorder, infection at the injection site, or pregnancy.

A computer generated sequence (GraphPad Software Inc, La Jolla, California) was used to randomize patients. Allocation was concealed in opaque sealed envelopes that were opened by the pri mary investigator just before performing the ISBPB. Patients were randomized into 1 of 2 study groups: The liposome bupivacaine group received 5 mL of 0.25% standard bupivacaine immedi ately followed by 10 mL of liposome bupivacaine (133 mg). The standard bupivacaine alone group received 15 mL of 0.25% standard bupivacaine.

Block Procedure

The ISBPB was performed preoperatively with ultrasound guidance and standard American Society of Anesthesiologists monitoring. Patients were placed in beach chair position with their head turned to the contralateral side. A high frequency (18 MHz) linear transducer (BK 3000, BK Medical, Analogic Ultrasound, Herlev, Denmark Ultrasound; Division of Analogic Ultrasound, Peabody, Massachusetts) was used to identify the interscalene space, and monitor needle placement and distribution of the local anesthetic. After local anesthetic infiltration of the skin (lidocaine 2%, 3 5 mL), an insulated block needle (Stimuplex Ultra, 0.7 × 50 mm; B. Braun Melsungen AG, Melsungen, Germany) was inserted in plane and advanced into the interscalene space between the C5 and C6 nerve roots. Electrical nerve stimulation (Stimuplex HNS 12; B. Braun Melsungen AG) and an in line injection pressure monitor (BSmart; B. Braun) were used to monitor needle placement and injection. To decrease the risk for needle nerve contact or injec tions into the roots of the brachial plexus, injections were halted when a motor response at 0.5 mA or less (0.1 millisecond) and/or opening injection pressure greater than 15 psi were present.[19] After negative aspiration, the study solutions were slowly injected over 2 to 3 minutes (approximately 10 mL/min). The same vol ume (15 mL) of injectate was used in both groups.

Intraoperative Procedures

After ISBPB, general anesthesia was induced and maintained with a target controlled infusion of propofol (3 4 μg kg ^{1}) and a continuous infusion of remifentanil (1 2 μg kg ^{1}·min ^{1}). Muscle relaxation at induction was obtained by a single bolus injection of rocuronium (0.6 mg kg ^{1}). No other opioids were allowed for an algesia during surgery. Patients were intubated and mechanically ventilated in a volume controlled manner (6 8 mL·kg ^{1}); lungs were ventilated with 50% O_2. End of anesthesia was defined as exit of the patient from the operating room after emergence from anesthesia. The multimodal analgesic regimen was initiated intra operatively and consisted of intravenous administration of para cetamol, 1 g; ketorolac, 0.5 mg/kg ^{1} with a maximum single dose of 30 mg; and dexamethasone, 5 mg. The regimen was con tinued postoperatively and consisted of oral administration of paracetamol, 1 g·6 h ^{1}; and ibuprofen, 400 mg·8 h ^{1}. Intravenous dexamethasone, 5 mg·24 h ^{1}, was continued for 48 hours. Tram adol, 50 mg, was prescribed sublingually every 4 hours as needed for breakthrough pain.

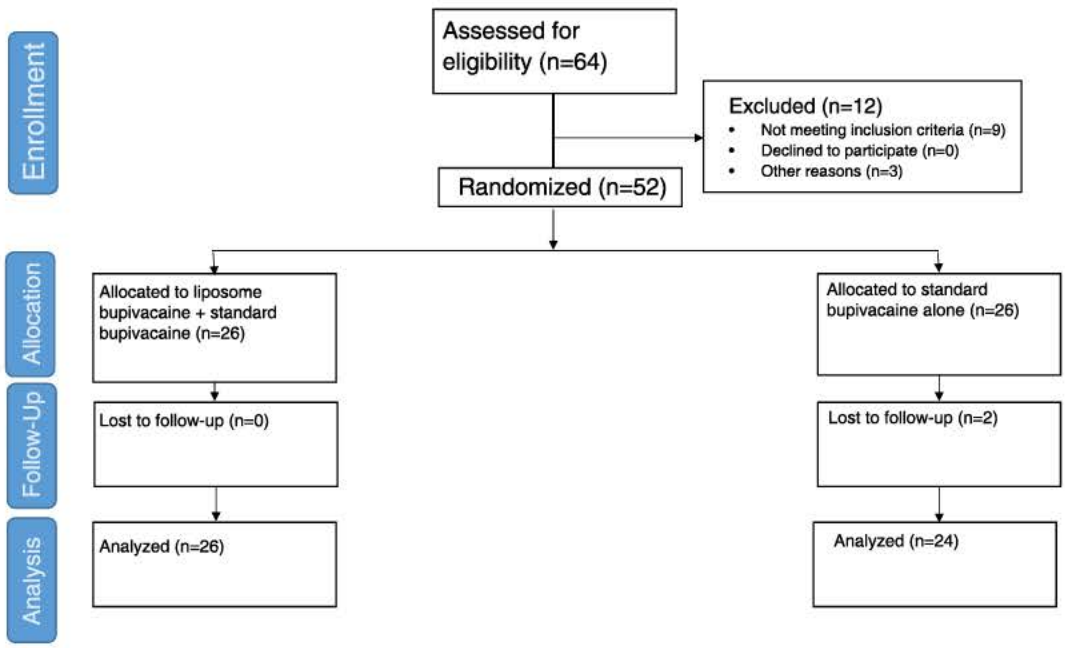

FIGURE 1. CONSORT diagram.

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Outcomes

Primary

The Modified Brief Pain Inventory (MBPI) Short Form was used to assess worst pain in the first postoperative week (POD1, POD2, POD3, POD4, and POD7).[20] Specifically, question 1 of the MBPI asks patients to rate pain at its WORST in the last 24 hours on an 11 point Numeric Rating Scale (NRS) ranging from zero (no pain) to 10 (pain as bad as you can imagine). The MBPI short form has been previously reported to be reliable, in ternally consistent over time, and to have good convergent and concurrent validity when administered daily for 1 week (days 1 7). Moreover, these findings held when the individual pain items of the MBPI (worst pain, average pain, and pain now) were tested.[20] Importantly, the item "Pain at its worst in the last 24 hours" fulfilled the expectations of the FDA Guidance for In dustry on the use of patient reported outcomes with regard to con ceptual framework, reliability, construct validity, and ability to detect clinically meaningful change.[21] The MBPI is shown in Ap pendix 1 (Supplemental Digital Content 1, http://links.lww.com/AAP/A189).

Secondary

Perspectives of studies examining the pain experience have broadened to include some functional and socioemotional compo nents.[20] Hence, we included satisfaction with pain treatment, functionality of the surgical arm, sleep duration, and postoperative use of opioids as secondary outcomes. Block characteristics and adverse effects were also included to confirm drug safety.

Satisfaction with pain treatment was reported on the Overall Benefit of Analgesia Score (OBAS) that was collected on POD1, POD2, POD3, POD4, and POD7. Total OBAS scores are ob tained from the 7 item OBAS (Supplemental Digital Content 2, http://links.lww.com/AAP/A190) by summing responses from the first 6 questions and adding the difference of 4 minus the re sponse to question 7, that is, summing Q1 through Q6 and adding (4 score from Q7); hence, lower total scores indicate more benefit.[22]

As there is no criterion standard for patient or physician as sessment of shoulder function, published measures were consid ered for their validity, reliability, applicability to our specific patient population, and response burden (understandability and ease of use). It was ultimately decided to adapt the scale of the Constant Murley score (CS) that has been recommended as the scoring system of the European Society of Shoulder and Elbow Surgery and has become the most commonly used outcome mea sure for assessing the impact of shoulder interventions. Moreover, it has been validated for rotator cuff repair and total shoulder arthroplasty. The CS domains of activities of daily living (work, recreation/sports, sleep) are each on a 6 point Likert scale from zero (worst) to 5 (best).[23,24] We combined these into a global scale of arm function that is on a 6 point Likert scale: zero, unable to use arm; 1, only slight activities possible; 2, able to do some daily ac tivities; 3, able to do most daily activities; 4, slight restrictions only; 5, normal activities.

Hand strength was measured using a dynamometer (Jamar, Duluth, Minnesota) that recorded maximum force in kilograms. Patients were asked to squeeze the handle of the dynamometer while keeping their elbow flexed at a right angle. Measurements were done bilaterally in triplicates, and their mean values were cal culated. An evaluator blinded to group assignment measured hand strength at baseline, 1 and 2 hours postoperatively, and at POD1.

Duration of sleep (hour) in the first postoperative week was obtained by phone calls to the patients on POD1, POD2, POD3, POD4, and POD7.

Sensory block in the shoulder area was assessed by pinprick with a paperclip in the distribution of the axillary nerve (skin of the deltoid area) and was rated on a scale of zero (no sensation) to 10 (normal sensation). Motor block of the deltoid muscle was rated on a scale of zero (no strength) to 10 (full strength) upon arm abduction. An evaluator blinded to group assignment ob tained sensory and motor block ratings at baseline and every 5 minutes until 30 minutes, and at 1, 2, 12, 24, and 48 hours (discharge POD1).

Use of opioids (recorded in a diary provided to the patients before discharge) and adverse effects, including sensory motor deficits, such as tingling, numbness, and weakness, were obtained by phone calls to the patients on POD2, POD3, POD4, and POD7.

Blinding

Liposome bupivacaine (opaque white) has a different appear ance than standard bupivacaine (clear colorless). At the time this study was conducted (July to December 2015), coadministration of liposome bupivacaine required separate injections, as the mixing of liposome bupivacaine with standard bupivacaine was not recommended by the FDA. Before treatment, assignment en velopes were opened by the primary investigator; all blinded staff were removed from the block room and remained out of the block room during drug administration. Surgeons were unaware of the assigned treatment, and every effort was made to ensure that pa tients were blinded to their treatment group. In particular, syringes with study medication were masked with cloth tape, making it im possible to distinguish between the treatment and placebo injectates. Moreover, a yellow pole tag denoting status as a re search subject warned staff that no discussion of the research was to occur in the patient's presence. Blinded staff conducted the sensory motor assessments after the block injections had been administered. The blinded staff conducted all patient follow up as sessments; unblinded staff were not present during the follow up assessments.

Statistical Analysis

The sample size for this study was based on the 11 point NRS for worst pain score in the last 24 hours as stated in the MBPI short form [from zero (no pain) to 10 ("pain as bad as you can imagine")]. As liposome bupivacaine is released gradually after administration, an arbitrary time point (POD2) was deemed ap propriate for sample size estimation. The pain categories of 0 to 3 (none to mild), 4 to 7 (moderate), and severe (8+) were used to guide selection of a minimal clinically important difference to detect. As 3 to 4 NRS points span these categories, a minimal clin ically important difference of 3 points was deemed important to detect, and with standard deviation 2.5, Type I error 0.01, and power 0.9, the sample size was estimated at 23 per group.[20] Three additional patients per group were included in the event of loss to follow up.

Generalized estimating equations (GEEs) with robust stan dard errors were used to examine differences between groups over time. The GEE is flexible with respect to type of outcome variable (including possibly skewed continuous distributions and ordinal measures) and to unequally spaced observations over time. For in stance, worst pain, total OBAS, and sleep duration were collected from POD1 to POD4 and then on POD7; in contrast, sensory and motor block were tested in 5 minute intervals until 30 minutes and then at 1, 2, 12, 24, and 48 hours. In GEE analyses, a conservative unstructured correlation structure was used in order not to assume the relative magnitude of correlation between any 2 pairs of obser vations (although GEE is robust against choosing an incorrect cor relation structure). Link function was identity for these continuous

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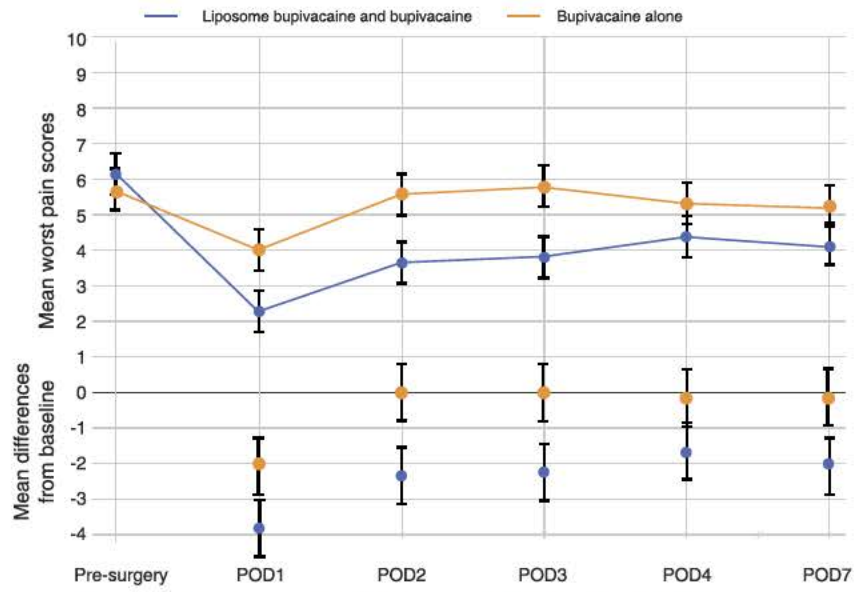

FIGURE 2. Worst pain scores (NRS mean ± SEM) at baseline, POD1, POD2, POD3, POD4, and POD7 in patients receiving ISBPB for shoulder surgery with 15 mL liposome bupivacaine added to standard bupivacaine (10 mL/133 mg liposome bupivacaine + 5 mL 0.25% standard bupivacaine) (n = 26) or 15 mL 0.25% standard bupivacaine alone (n = 24) for postoperative pain management. Differences from worst pain at baseline (NRS mean ± SEM) are also graphed for POD1, POD2, POD3, POD4, and POD7 by group.

TABLE 1. Sociodemographic Characteristics and Clinical Features of 50 Patients Undergoing ISBPB for Major Shoulder Surgery With 15 mL Liposome Bupivacaine Added to Standard Bupivacaine (10 mL/133 mg Liposome Bupivacaine + 5 mL 0.25% Standard Bupivacaine) (n = 26) or 15 mL 0.25% Standard Bupivacaine Alone (n = 24) for Postoperative Pain Management

	Liposome Bupivacaine + Standard Bupivacaine (n = 26)	Standard Bupivacaine (n = 24)	Standardized Differences For Continuous Variables
Sex, M:F	13:13	10:14	
Age, y	61 ± 11	57 ± 12	4 ± 3
Body mass index, kg/m^2	28 ± 4	27 ± 5	1.7 ± 1.3
ASA physical status			
I	6 (23)	7 (29)	
II	19 (73)	17 (71)	
III	1 (4)	0	
Surgical side, R:L	14:12	18:6	
Surgery type			
Rotator cuff	20 (77)	20 (83)	
Shoulder replacement	6 (23)	4 (17)	
Hand strength of surgical arm, kg	27 ± 13	27 ± 12	0.4 ± 3.5
Functionality of surgical arm			
Unable to use	0	0	
Only light activity	6 (23)	4 (17)	
Able to do some activities	4 (15)	8 (33)	
Able to do most activities	9 (35)	7 (29)	
Slight restrictions only	7 (27)	4 (17)	
Normal	0	1 (4)	
Worst pain in last 24 h (NRS)*	6.1 ± 2.8	5.8 ± 3.0	0.4 ± 0.8
Pain relief by medication(s) in last 24 h (%)†	54 ± 32	46 ± 27	8.2 ± 9.4

Data are mean ± SD for continuous variables, and n (%) for discrete (nominal, ordinal) variables.

*Modified Brief Q1 asks the patient to mark the number that best describes his/her pain at its *worst* in the last 24 hours on NRS from zero (no pain) to 10 ("pain as bad as you can imagine").

†Modified Brief Q5 asks the patient to mark percent pain relief (from 0% to 100% in 10% increments) from medications in the last 24 hours.

ASA indicates American Society of Anesthesiologists.

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outcome measures. In addition, since pain is a subjective phenom enon, each patient served as his/her own control when evaluating pain differences from baseline at each time point by group (Fig. 2). *P* values from these *t* tests were Bonferroni adjusted for multiple comparisons (0.05/5 0.01).

Tests of differences between groups for reported adverse ef fects were not planned as the number of *each* adverse effect was anticipated to be small, and patients could report more than one adverse effect. Instead, the relative risk (with 95% confidence in terval [CI]) for at least one adverse effect within the first postoper ative week was reported.

All analyses were performed using IBM SPSS Statistics for Windows (version 22.0; IBM Corp, Armonk, NY).

RESULTS

Two patients, both randomly assigned to the standard bupiva caine alone group, were excluded, as data collection during the follow up period was inadvertently missed (Fig. 1). The groups did not differ in their sociodemographic characteristics or clinical features. Before surgery, most patients reported at least some restrictions in the use of their surgical extremity. At baseline, worst pain in the last 24 hours was generally rated as moder ately high, but patients in both groups reported approximately 50% relief from their pre enrollment analgesic regimen in the last 24 hours (Table 1).

Worst Pain

When compared with pain before surgery (baseline), the groups did not differ at any of the postoperative days studied (Fig. 2). Worst pain scores (NRS) were consistently lower in the first post operative week for patients given liposome bupivacaine added to standard bupivacaine than for patients given standard bupivacaine alone (GEE, Wald χ^2, *P* 0.001) (Fig. 2). However, the overall difference was modest (estimated marginal mean values, 3.6 ± 0.3 vs 5.3 ± 0.4 points on the NRS, respectively; difference, 1.6 ± 0.5; 95% CI, 0.8 2.5).

TABLE 2. Total Overall Benefit of Analgesia Score (OBAS), Functionality in the Surgical Arm, Sleep Duration, and Opioid Consumption of Patients Undergoing ISBPB for Major Shoulder Surgery With 15 mL Liposome Bupivacaine Added to Standard Bupivacaine (10 mL/133 mg Liposome Bupivacaine + 5 mL 0.25% Standard Bupivacaine) (n = 26) or 15 mL 0.25% Standard Bupivacaine Alone (n = 24) for Postoperative Pain Management

	Postoperative Day (POD)				
	POD1	POD2	POD3	POD4	POD7
OBAS (total)*					
Liposome bupivacaine + standard bupivacaine	1.4 ± 2.1	1.8 ± 1.9	2.0 ± 2.9	2.2 ± 2.2	1.9 ± 2.3
Standard bupivacaine	2.8 ± 2.8	3.3 ± 2.7	3.2 ± 2 2	3.6 ± 2.8	3.3 ± 3.2
Unadjusted *t* test *P* value	0.05	0.03	0.12	0.05	0.08
Functionality of surgical arm†					
Liposome bupivacaine + standard bupivacaine					
Unable to use		6 (23)	2 (8)	2 (8)	1 (4)
Only light activity		10 (39)	7 (27)	4 (15)	2 (8)
Able to do some activities		7 (27)	11 (42)	13 (50)	13 (52)
Able to do most activities		0	2 (8)	3 (12)	6 (24)
Slight restrictions only		2 (8)	3 (12)	3 (12)	2 (8)
Normal		1 (4)	1 (4)	1 (4)	1 (4)
Standard bupivacaine					
Unable to use		5 (21)	2 (9)	3 (13)	3 (12)
Only light activity		11 (46)	7 (30)	7 (30)	3 (12)
Able to do some activities		6 (25)	7 (30)	5 (22)	9 (38)
Able to do most activities		2 (8)	3 (13)	3 (13)	3 (12)
Slight restrictions only		0	3 (13)	3 (13)	4 (17)
Normal		0	1 (4)	2 (9)	2 (8)
Unadjusted χ^2 *P* value		0.4	1.0	0.4	0.6
Sleep duration, h					
Liposome bupivacaine + standard bupivacaine	4.5 ± 0.5	5.0 ± 0.4	5.4 ± 0.4	5.8 ± 0.4	6.1 ± 0.3
Standard bupivacaine	4.9 ± 0.6	5.5 ± 0.5	5.4 ± 0 5	5.6 ± 0.5	5.5 ± 0.5
Unadjusted *t* test *P* value	0.7	0.4	1.0	0.8	0.3
Opioid (tramadol) consumption, mEq					
Liposome bupivacaine + standard bupivacaine	0.6 ± 0.6	2.6 ± 0.9	2.3 ± 0.8	2.5 ± 0.8	2.4 ± 0.9
Standard bupivacaine	0.4 ± 0.3	1.6 ± 0.6	3.2 ± 1.4	2.7 ± 1.0	2.6 ± 0.8
Unadjusted *t* test *P* value	0.8	0.3	0.5	0.9	0.9

*Total OBAS score: sum items Q1 through Q6 and add [4 score from Q7]; hence, lower total scores indicate more benefit.

†Functionality of surgical arm was not assessed on POD1.

Descriptive data with unadjusted *P* values are mean ± SEM for continuous variables, and n (%) for ordinal variables at hospital discharge (POD1) and during the first postoperative week (POD2, POD3, POD4, and POD7).

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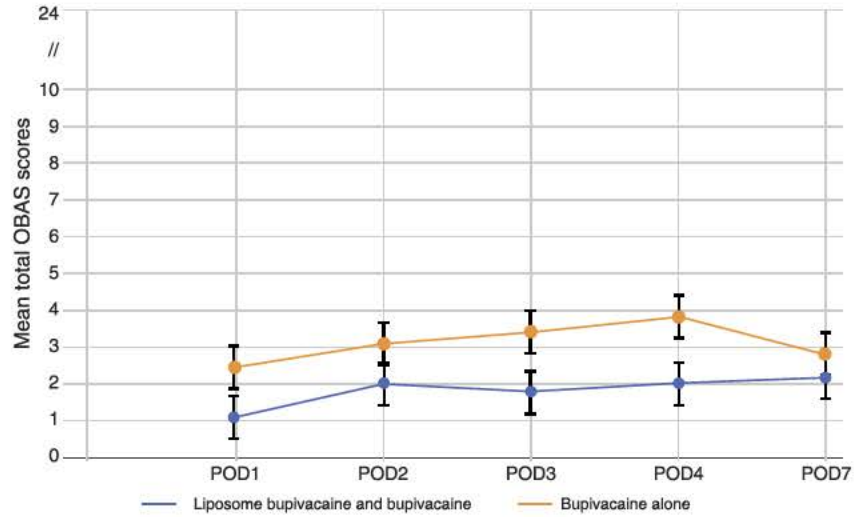

FIGURE 3. Total OBAS (mean ± SEM) at POD1, POD2, POD3, POD4, and POD7 by group. Lower scores indicate higher satisfaction with postoperative pain management.

Satisfaction With Pain Management

Lower OBAS total scores indicate greater benefit and were consistently lower for patients given liposome bupivacaine added to standard bupivacaine than for patients given standard bupivacaine alone (GEE, Wald χ^2, P 0.004) (Table 2); the overall difference was modest (estimated marginal mean values, 1.8 ± 0.3 vs 3.3 ± 0.4 points on the OBAS total score, respectively; difference, 1.4 ± 0.5; 95% CI, 0.5 2.4) (Fig. 3).

Functionality and Hand Strength

Per institutional protocol, the surgical arm could not be mobilized for 24 hours; thus, functionality could not be measured on POD1. However, functionality did not differ between the groups through the remainder of the first postoperative week (GEE, Wald χ^2, P 0.40) (Table 2).

Hand strength (kg) varied over time but was similar between the groups throughout the interval of data collection. Specifically, hand strength decreased to 6.8 ± 4.3 kg (for both groups) by 1 hour and rose to 17.5 ± 11.1 kg (for both groups) by POD1.

Sleep Duration

In the first postoperative week, sleep duration did not differ between patients given liposome bupivacaine added to standard bupivacaine and patients given standard bupivacaine alone (GEE, Wald χ^2, P 0.7; estimated marginal mean values, 5.4 ± 0.3 vs 5.3 ± 0.3 hours, respectively) (Table 2).

Sensory and Motor Characteristics

Block onset time (minutes) did not differ significantly between patients given liposome bupivacaine added to standard bupivacaine and patients given standard bupivacaine alone, 24.5 ± 20.9 vs 14.4 ± 7.3 minutes, respectively (P 0.17); mean difference ± SEM, 10 ± 7 minutes, 95% CI, 25 to 5 minutes.

Shoulder sensation and motor abduction did not differ between the groups over time (GEE, Wald χ^2, P 0.9 and P 0.7, respectively) (Table 3).

Opioid Consumption, Adverse Effects

Time to first request for opioids did not differ between patients given liposome bupivacaine added to standard bupivacaine

TABLE 3. Sensory and Motor Scores by Group Over Time

	0 min	5 min	10 min	15 min	20 min	25 min	30 min	1 h	2 h	12 h	24 h	48 h
Sensory												
Liposome bupivacaine added	9.5 ± 0.2	7.5 ± 0.5	6.5 ± 0.6	5.9 ± 0.6	4.6 ± 0.5	3.7 ± 0.4	3.0 ± 0.4	1.9 ± 0.4	2.7 ± 0.6	4.1 ± 0.7	6.5 ± 0.8	6.7 ± 0.8
Standard bupivacaine only	9.4 ± 0.2	7.0 ± 0.5	5.5 ± 0.6	4.4 ± 0.5	2.7 ± 0.5	1.6 ± 0.3	1.1 ± 0.3	1.6 ± 0.4	2.4 ± 0.6	3.9 ± 0.7	7.5 ± 0.7	7.7 ± 0.7
Motor												
Liposome bupivacaine added	8.3 ± 0.6	7.3 ± 0.6	6.5 ± 0.6	5.6 ± 0.7	4.7 ± 0.7	4.2 ± 0.7	4.0 ± 0.6	1.0 ± 0 3	1.2 ± 0.3	1.5 ± 0.4	3.1 ± 0.6	3.6 ± 0.7
Standard bupivacaine only	7.3 ± 0.7	5.7 ± 0.6	4.1 ± 0.7	3.0 ± 0.7	2.5 ± 0.6	1.9 ± 0.6	1.8 ± 0.6	0.7 ± 0 2	0.9 ± 0.2	1.1 ± 0.3	4.1 ± 0.6	4.4 ± 0.6

Data are mean ± SEM.

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TABLE 4. Adverse Effects Reported by Patients Undergoing ISBPB for Major Shoulder Surgery With 15 mL Liposome Bupivacaine Added to Standard Bupivacaine (10 mL/133 mg Liposome Bupivacaine + 5 mL 0.25% Standard Bupivacaine) (n = 26) or 15 mL 0.25% Standard Bupivacaine Alone (n = 24) for Postoperative Pain Management

Adverse Effect*	Liposome Bupivacaine + Standard Bupivacaine (n = 26)	Standard Bupivacaine (n = 24)
Unique patients reporting adverse effects†	17 (65)	10 (42)
Hoarseness	14 (82)	7 (70)
Dizziness	5 (29)	4 (40)
Ear ringing	3 (18)	1 (10)
Metallic taste	1 (6)	2 (20)
Shortness of breath		4 (40)
Vision impairment	1 (6)	
Pulmonary embolism‡	1 (6)	

Data are descriptive, n (%).

*Total percentages do not sum to 100%, as some patients reported more than 1 adverse effect; percentages of specific adverse effects are based on n 17 and n 10 who reported adverse effects in the liposome bupivacaine added to standard bupivacaine and the standard bupivacaine alone groups, respectively.

†Relative risk for at least 1 adverse effect 1.6 (95% CI, 0.9 2.7).

‡This patient had an extensive workup. The source of the adverse effect was determined to be deep venous thrombosis in the lower extremity that occurred unrelated to study treatment.

and patients given standard bupivacaine alone, 43.3 ± 39.4 vs 46.3 ± 41.0 hours, respectively (P 0.8). Total tramadol (mEq) consumption in the first postoperative week did not differ between the groups, 16.7 ± 21.9 vs 23.7 ± 23.4 mEq, respectively (shown by POD in Table 2).

All adverse effects were reported on POD1 (Table 4). Seven teen patients given liposome bupivacaine added to standard bupiv acaine (65%) and 10 patients given standard bupivacaine alone (42%) reported adverse effects. Risk for complications was not elevated in patients given the liposome bupivacaine mix ture (RR, 1.6; 95% CI, 0.9 2.7).

DISCUSSION

Over the first postoperative week, worst pain scores were lower in patients given liposome bupivacaine added to standard bupivacaine than in patients given standard bupivacaine alone. However, these modest findings did not translate into improvements in pain com pared with baseline, reductions in opioid consumption, or sleep quality. It is possible that the observed differences could be greater in patients who have contraindications to some elements of multi modal analgesia therapy, such as to nonsteroidal anti inflammatory drugs (eg, renal or upper gastrointestinal disease), dexamethasone (diabetes), or acetaminophen (liver disease). The observed effect in the postoperative interval studied may be related to sympathetic blockade from the gradual release of small amounts of bupivacaine base as the liposomes degrade. Unfortunately, detailed sensory as sessments in our study were hindered by the clinical setting and the presence of surgical dressings, ice cooling, and/or tissue swell ing of the arm from water instillation during shoulder surgery.

In addition, the absence of immediately available opioid treatment via intravenous patient controlled analgesia makes it challenging to establish the relationship between intervention (eg, ISBPB) and analgesia using oral opioids. There may be mul tiple obstacles and delays in patients' requests for oral opioids and their delivery by nurses, such as in the presence of nausea and the inability to take pills. Oral opioid therapy can be even more vari able at night when nursing staff is less.

Interscalene brachial plexus block results in phrenic nerve block in many patients; however, most studies that report high incidence of phrenic blockade have used higher volumes or concentrations of local anesthetics.[25–27] In our study, none of the patients reported prolonged respiratory symptoms. As with the study of liposome bupivacaine in femoral nerve block, we did not record any neurologic adverse effects or complications that could be due to the toxicity of the liposome bupivacaine mixture.[17]

We chose to combine liposome bupivacaine with standard bupivacaine in our study because pharmacokinetic studies indi cated that the plasma level of bupivacaine rises significantly only after 16 to 24 hours after application.[18] Although the plasma level of local anesthetic may not be indicative of the amount of drug available at the injection site to effect neural blockade, its pharma codynamic effects as assessed by plasma levels should correlate with the release of drug locally. We reasoned that since the suspen sion of liposome bupivacaine contains 3% [7.98 mg] free bupivacaine (of 266 mg contained in liposomes), 10 mL of the suspension could have only 4 mg of the free drug, which may not be sufficient for effective ISBPB. Therefore, assuming an adequate quantity of the drug would be released from liposomes after 16 to 72 hours,[17,18] we injected 10 mL of liposome bupivacaine immediately after injection of 5 mL of 0.25% standard bupivacaine (12.5 mg) to achieve an early onset peripheral nerve block until active drug is released. However, we had no data to guide the dosing of lipo some bupivacaine for interscalene blockade when making this methodologic choice; rather, our dosing was based on clinical ob servations during infiltration of liposome bupivacaine into the sur gical site, and we chose a fixed sequenced injection of 0.25% standard bupivacaine and liposome bupivacaine to constitute the combined 15 mL volume commonly used for ISBPB. Nonethe less, it is possible that different volumetric ratios of liposome bu pivacaine and standard bupivacaine and/or different concentrations of standard bupivacaine may alter our findings. Of note, at the time our study was conducted, mixing standard bupivacaine with lipo some bupivacaine was not recommended by the FDA; therefore, we injected liposome bupivacaine immediately *after* injecting standard bupivacaine using 2 different syringes in a sequenced in jection process. Consequently, we do not know whether mixing standard bupivacaine with liposome bupivacaine, which is now allowed in the drug label, would yield similar results.

In conclusion, patients having ambulatory major shoulder surgery experience prolonged moderate to severe pain in the set ting of a multimodal approach to analgesia and peripheral nerve

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block with or without the addition of liposome bupivacaine to standard bupivacaine. The addition of liposome bupivacaine to standard bupivacaine may lower pain in the first postoperative week even in the setting of multimodal analgesia for major shoul der surgery. Enhanced patient's satisfaction with pain manage ment in the same postoperative interval seems to support this finding. Future dose ranging studies of the liposome bupivacaine standard bupivacaine mixture are indicated to determine optimal dosing and mixture regimens that prolong postoperative analgesia after major shoulder surgery. Likewise, research is needed to de termine whether the addition of liposome bupivacaine in ISBPB can lead to reductions in opioid use, improvements in physical therapy, and reductions in expenditures related to pain manage ment (ie, hospital readmission).

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EXHIBIT B

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Original Research

Effect of Bupivacaine Liposome Injectable Suspension on Sensory Blockade and Analgesia for Dupuytren Contracture Release

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collagenase *Clostridium histolyticum*
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forearm block

Purpose: To study the efficacy of bupivacaine liposome injectable suspension in prolonging sensory blocks of the median and ulnar nerves for subjects with Dupuytren contracture release by collagenase injection. We hypothesized that combining liposome bupivacaine and bupivacaine hydrochloride would extend the duration of blocks without added complications.

Methods: We randomized 32 subjects scheduled for Dupuytren contracture release with collagenase *Clostridium histolyticum* injections to receive forearm blocks of the median and ulnar nerves with a mixture of 5 mL liposome bupivacaine 1.33% plus 2.5 mL bupivacaine hydrochloride 0.5% per nerve (n = 16) or 7.5 mL bupivacaine hydrochloride 0.5% alone per nerve (n = 16). Sensory block and analgesia were assessed through the first posttreatment week.

Results: Sensory block was nearly 4 times longer in subjects who received the liposome bupivacaine mixture compared with subjects who received bupivacaine hydrochloride alone. Most subjects (13 of 16) who received the liposome bupivacaine mixture had adequate analgesia for finger manipulation to rupture the cords, whereas most subjects (15 of 16) who received bupivacaine hydrochloride alone required additional anesthesia. Subjects in the liposome mixture group reported lower pain scores through the first 3 days after treatment. There were no serious side effects.

Conclusions: Addition of liposome bupivacaine to forearm blocks for Dupuytren contracture release prolonged sensory block and improved pain scores without increasing side effects or impairing hand function. Supplemental lidocaine injections for the painful phases of Dupuytren contracture release with collagenase *C histolyticum* injections were not required by most subjects who received liposome bupivacaine.

Type of study/level of evidence: Therapeutic I.

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Dupuytren contracture is a common disease of the connective tissue of the hand in which the formation of subcutaneous nodules and cords causes disabling flexion contracture of one or more fingers.[1,2]

The cords of these contractures can be enzymatically weakened after injection of collagenase *Clostridium histolyticum* (CCH), allowing the fingers to be manipulated to break up the cords.[3]

Pain is caused by multiple injections of collagenase into the cords (phase 1 of treatment), during manipulation of the fingers to break up the cords (phase 2, 24 to 72 hours after injection), and from the inflammatory response, which can last several days.[4] Ideal analgesia would provide adequate pain relief for all phases of treatment (Fig. 1). Although forearm (median and ulnar) nerve blocks can provide adequate analgesia for phase 1 of treatment, they have a relatively short duration.[5,6]

Declaration of interests: Admir Hadzic serves a consultant for Pacira Pharmaceuticals and has received consulting honoraria and educational and research grants. No benefits in any form have been received or will be received by the other authors related directly or indirectly to the subject of this article.

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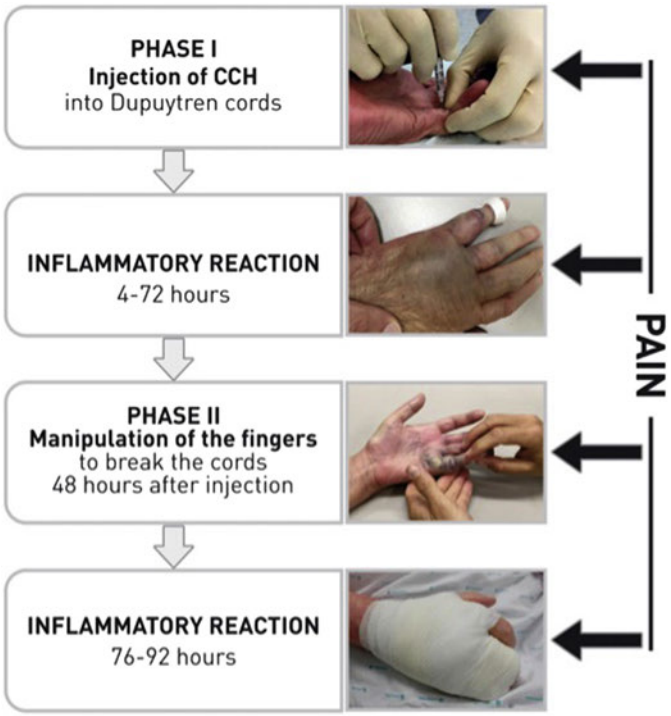

Figure 1. Phases of treatment in Dupuytren contracture release with CCH injections.

A recent study[4] reported that 43% of patients had severe pain during finger manipulation even when analgesia was provided with a wrist block (10 mL of 2% mepivacaine); 53% of patients had pain after injection of collagenase despite treatment with an oral analgesic combination of acetaminophen 650 mg, ibuprofen 600 mg, or metamizole 575 mg every 8 hours. Bupivacaine liposome injectable suspension (EXPAREL, Pacira Pharmaceuticals, Inc, Par sippany, NJ) is an extended release formulation of a local anesthetic that has been approved by the Food and Drug Administration for infiltration into the surgical wound, and recently (April, 2018) for use in interscalene brachial plexus blocks. Although the efficacy of liposome bupivacaine for postoperative pain has been studied with respect to soft tissue infiltration,[7] it has not been examined in the median and ulnar nerve blocks of the forearm. Thus, although local blocks can be used for CCH treatment of Dupuytren contracture, we chose forearm nerve blocks to study the effects of liposome bupi vacaine in the small peripheral nerves.

The objective of this study was to evaluate the analgesic benefit of liposome bupivacaine in prolonging forearm blocks of the me dian and ulnar nerves and analgesia for subjects with Dupuytren contracture release with injections of CCH into the affected cords. We primarily tested the hypothesis that adding liposome bupiva caine in forearm blocks would sufficiently prolong the sensory block to provide adequate pain relief for Dupuytren contracture release with CCH. We secondarily tested the hypothesis that adding liposome bupivacaine in forearm blocks would improve pain scores in the first posttreatment week.

Materials and Methods

This double blind, randomized, controlled trial was approved by the Ethics Committee of Ziekenhuis Oost Limburg, Genk, Belgium (16/011), and by FAGG, the Belgian federal agency for medicines and health products (2016 001656 22). The trial was registered at www.clinicaltrials.gov (NCT03106519) in March, 2017. Patients scheduled for Dupuytren contracture release who were aged 18 to 85 years, had an American Society of Anesthesiologists physical status of I to III, and were able to understand the purpose and risks of the study were eligible to participate. Patients were excluded if they were pregnant, had a history of allergic or adverse reaction to local anesthetics, used pain medications within 28 hours before treatment, had a suspected or known recent history (less than 3 months) of drug or alcohol abuse, had an infection at the planned block site, had a body mass index greater than 44 kg/m^2, or had any chronic condition or psychiatric disorder that could compromise neurological or study assessments.

Consenting subjects were randomized in a computer generated 1:1 ratio to receive a mixture of 5 mL bupivacaine liposome injectable suspension 1.33% plus 2.5 mL bupivacaine HCl 0.5% or 7.5 mL bupivacaine HCl 0.5% alone to the median and ulnar nerves before CCH injection (Xiapex, Swedish Orphan Biovitrum, AB, Stockholm, Sweden). Each subject received a total drug volume of 15 mL (7.5 mL/nerve). The traditional bupivacaine HCl used in common clinical practice was mixed with the extended release formulation of liposome bupivacaine (EXPAREL). This model has been used to facilitate early interscalene brachial plexus block onset and prolong block duration.

After treatment, all subjects received the standardized multi modal regimen for pain control with acetaminophen 1 g every 6 hours and diclofenac 75 mg 2 times daily. Transmucosal tramadol 50 mg (every 6 hours as needed) was used for breakthrough pain. In addition, subjects received rescue medication upon request for breakthrough pain or as necessary upon discharge home.

Anesthesiology staff members performing the nerve blocks were not blinded to drug treatment but did not participate in subject assessments. Surgeons and research personnel were blin ded to drug treatment because blocks were performed in a separate procedure room outside the operating theater. Subjects were not told their allocated treatment. A strict blind was maintained so that the surgeon (who injected CCH and then manipulated the fingers) and the research personnel (who conducted the follow up assess ments of the subjects) would not know the assigned drug arms. The use of supplementary local anesthesia was based on subject request for pain relief and not the surgeon's perception of need. Subjects left the hospital facility on the same day of the CCH injection.

Nerve blocks

Study medication (bupivacaine liposome injectable suspension mixed with bupivacaine HCl or bupivacaine HCl alone) was administered at least 30 minutes before CCH injection and was deposited in the tissue plane around the median and ulnar nerves at the level of the mid forearm. All blocks were administered under ultrasound guidance. The injectate was deemed adequately distributed when it encircled the nerve, as documented by ultrasound.

The forearm blocks were the sole anesthetic modality for the CCH injections and were administered without premedication. We chose to use a more proximal approach to median and ulnar nerve blocks at the level of the forearm because a more distal approach (wrist blocks) failed to provide analgesia during finger manipula tion in 43% of patients in a study by Sanjuan Cerveró et al.[4]

Time to onset and offset of sensory blockade was tested in 5 minute intervals from injection of the study medication up to 30 minutes, and hourly thereafter until discharge. Sensory block onset was defined as time from end of each block procedure to no sensation in the median and ulnar nerve distributions. Sensory block duration was defined as time from block onset to time to return of complete sensation. Block success or failure was defined

as absence or presence of full sensation in the areas and muscles supplied by the median and ulnar nerves as assessed by pinprick.[8] Inadequate analgesia for phase 2 (finger manipulation to break up the cords) was defined as the need for additional injections of lidocaine 1% into the affected tissues of the hand to allow for effective manipulation and cord breakage.

Vital signs (blood pressure, heart rate, and oxygen saturation) were monitored every 3 minutes for the first 30 minutes after the block, every 5 minutes up to 1 hour after the block, and every 15 minutes until discharge. We obtained 12 lead electrocardiograms before block and approximately 2 hours after nerve blocks.

Posttreatment assessments

Worst pain (modified Brief Pain Inventory) was reported as a numeric rating scale (NRS) score ranging from 0 (no pain) to 10 (most extreme pain).[9] The NRS was recorded before and after block.

Before discharge home, subjects were given clear instructions regarding scheduling and questions that would be asked during the posttreatment telephone interviews. Specifically, subjects were trained to assess sensation and distinguish among complete sensation, light touch, and no sensation. They were also trained to assess the presence or absence of weakness in the blocked hand. Subjects were given a daily diary in which to record the NRS score before taking each dose of rescue medication (tramadol). The blinded research staff used standardized scripts to collect pain scores via phone interviews at 24 hours (D1 am), 36 hours (D1 pm), 48 hours (D2 am), 60 hours (D2 pm), 72 hours (D3 am), and 84 hours (D3 pm), and at D4, D5, D6, and D7. The worst pain was asked as question 1 from the modified Brief Pain Inventory: "Please rate your pain at its worst in the last 24 hours from 0 (no pain) to 10 (pain as bad as you can imagine)." This item, based on the NRS, was already familiar to subjects because it was asked during screening and in phase 1 of the study. The phone interview inquired about numbness and weakness or dysesthesias.

Polystyrene foam cups were given to subjects to take home upon discharge; subjects were instructed that use of these cups referred to use with the operated hand. The functionality of the hand was assessed by asking subjects, "Are you able to use a polystyrene foam cup?" Training in motor assessments using the polystyrene foam cup was done before the research intervention and repeated before discharge home. In addition, we assessed the presence or absence of the sensory and motor block by asking the patient to report numbness and/or weakness in the operated hand every 12 hours. At the 48 hour visit, the presence or absence of sensory block and hand weakness of the intrinsic muscles were evaluated, as well as the ability to use the polystyrene foam cup.

Subjects returned for finger manipulation and cord rupture 48 hours after the CCH injections. Lidocaine 1% was injected if the subject reported pain during manipulation of the fingers.

Side effects were recorded through day 7, including nausea, vomiting, fever, constipation, severe itching of the skin, dizziness, sleepless nights, excessive sweating, urinary retention, headache, and heart palpitations.

Statistical analysis

The sample size calculation, estimated on duration of sensory block, assuming a minimum difference important to detect at 48 hours (SD, 32 hours), α .01, and power of .90, yielded 15 subjects/group. This was increased to 16 subjects/group to accommodate block failures and losses to follow up. If bupivacaine liposome injectable suspension is capable of prolonging nerve block, its pharmacokinetic data suggest that the formulation should have a conduction block at least 48 hours longer than non encapsulated bupivacaine HCl, the active component of liposome bupivacaine.[10] We selected the SD of 32 hours because there is substantial vari ability in duration of nerve blocks with the currently available local anesthetics. Because liposome bupivacaine is an encapsulated formulation that releases an active substance, over 72 hours, an even wider variability in block duration might be anticipated.

Continuous variables are presented as means (SD) and cate gorical (nominal and ordinal) variables as n (%) or as a ratio as in gender and treated limb laterality. Duration of sensory and motor block was compared between groups by Student *t* test or Mann Whitney U test, as appropriate.

The proportions of subjects requiring additional anesthesia for phase 2 of treatment were compared between groups by chi square test.

Efficacy analyses followed intent to treat principles. Worst pain was analyzed by generalized estimating equations (GEE) to examine group differences over time. The GEE method is flexible with respect to the type of outcome variable (including possibly skewed continuous distributions and ordinal measures) and to observations that are unequally spaced over time. For instance, worst pain is reported at discharge (D0 pm), at D1 am and pm, D2 am and pm, and D3 am and pm, and then on D4, D5, D6, and D7. In the GEE analyses, a conservative unstructured correlation structure was used so as not to assume the relative magnitude of correlation between any 2 pairs of observations (although GEE is robust against choosing an incorrect correlation structure). Link function was identity for these continuous outcome measures.

Tests of differences between groups for reported side effects were not planned, because the number of each side effect was anticipated to be small, and subjects could report more than one side effect. Instead, the relative risk (with 95% confidence interval) for at least one side effect through day 7 was reported.

$P < .05$ was deemed statistically different.

Results

We assessed 55 patients for eligibility; 32 were randomly assigned (16/group) (Fig. 2). The groups did not differ in socio demographic characteristics or severity of disease (Table 1).

Duration of sensory block was significantly longer in the lipo some bupivacaine mixture group compared with the bupivacaine HCl—alone group (3.8 [1.1] vs 1.0 [0.3] days, respectively; $P < .001$). Additional anesthetic intervention to complete phase 2 of treat ment was required by 15 of 16 subjects (94%) who received bupi vacaine HCl alone, compared with 3 of the 16 subjects (20%) who received the liposome bupivacaine mixture ($P < .001$). Hence, no additional anesthesia was required in 80% of subjects who received the liposome bupivacaine mixture.

Previous pharmacokinetic analyses in femoral nerve block demonstrated that the peak concentration of liposome bupivacaine occurs during the first 72 h interval.[10,11] In the current study, subject reported worst pain (modified Brief Pain Inventory ques tion 1) over the first 3 posttreatment days was analyzed. General ized estimating equations (GEE) showed that pain over this interval was significantly lower in subjects who received the liposome bupivacaine mixture compared with those who received bupiva caine HCl alone (GEE P .010) (Fig. 3).

All subjects underwent a multimodal oral pain regimen throughout the study period. Three subjects took tramadol through day 7 for breakthrough pain: 2 in the liposome bupivacaine mixture group (total dose of 400 and 150 mg, respectively) and one in the bupivacaine HCl—alone group (100 mg).

Among subjects who received bupivacaine HCl alone, the pro portion who reported numbness decreased rapidly within the first 48 hours. In contrast, numbness appeared to persist through days 3

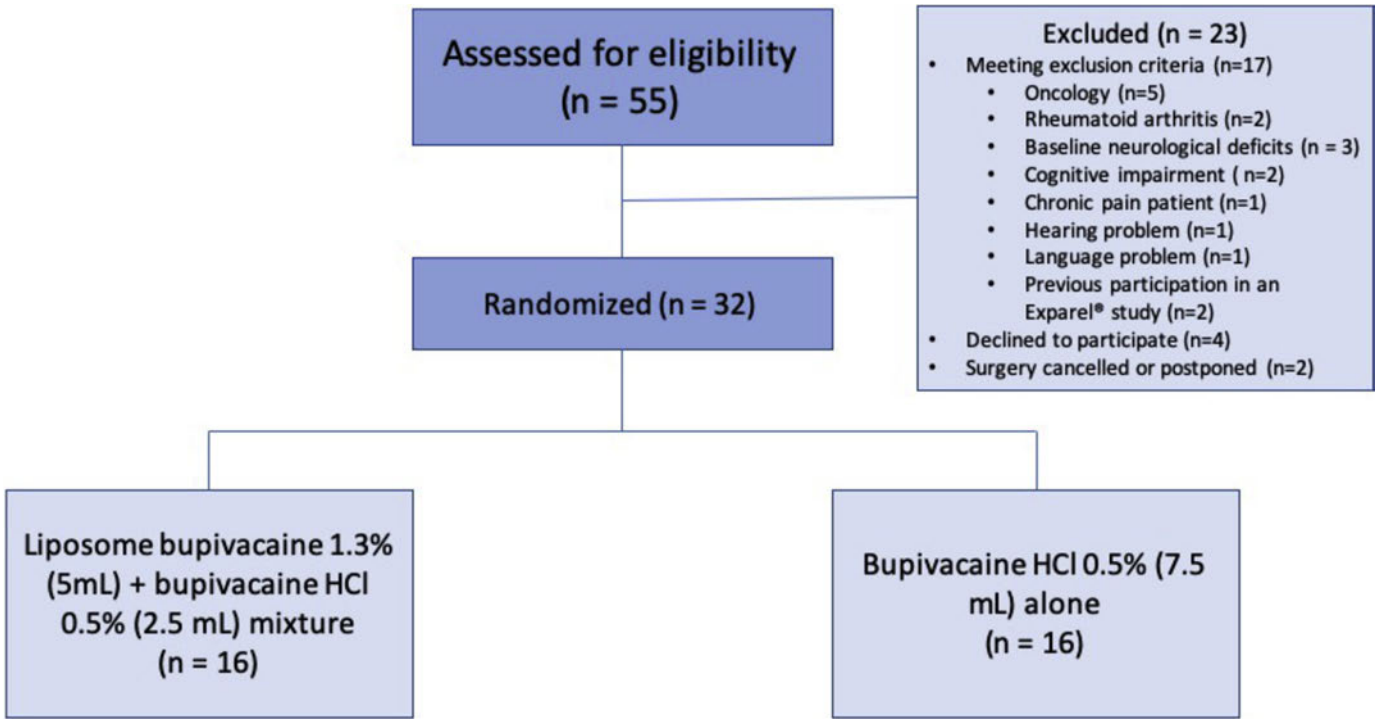

Figure 2. Consolidated Standards of Reporting Trials diagram for 2-arm study of bupivacaine liposome injectable suspension mixed with bupivacaine HCl or bupivacaine HCl alone.

Table 1
Sociodemographic Characteristics and Clinical Features of 32 Patients Undergoing Forearm Blocks of Median and Ulnar Nerves for Dupuytren Contracture Release

Demographics, pain, and arm functionality before surgery	Mixture of 5 mL Liposome Bupivacaine 1.3% Plus 2.5 mL Standard Bupivacaine 0.5% (per Median and Ulnar Nerve) (n 16)	7.5 mL Standard Bupivacaine 0.5% per Median and Ulnar Nerve) (n 16)
Gender (M : F)	14 : 2	14 : 2
Age, y (range)	66.2 (48 76)	63.5 (35 82)
Body mass index, kg/m^2*	25.7 (0.05)	26.5 (0.04)
Race (%)		
American Indian/Alaska native	0	0
Asian	0	0
Black/African American	0	0
Native Hawaiian/Pacific Islander	0	0
White	16 (100)	16 (100)
Other	0	0
American Society of Anesthesiologists physical status (%)		
I	4 (25)	7 (44)
II	10 (63)	8 (50)
III	2 (12)	1 (6)
Surgical side (R : L)†	3 : 13	8 : 8
Functionality of surgical hand (before surgery) (%)		
Unable to use	0	0
Only light activity	0	0
Able to do some activities	0	0
Able to do most activities	0	1 (6)
Slight restrictions only	8 (50)	6 (38)
Normal	8 (50)	9 (56)
NRS (0 10)		
At rest	0.6 (2.0)	0.2 (1.0)
During movement	1.5 (2.4)	0.4 (0.9)

Data are shown as means (SD) or mean (range) for continuous variables and n (%), ratio, or median (range) for discrete (nominal, ordinal) variables.
* Body mass index was missing for one subject (active comparator group).
† Pearson chi-square (2-sided) *P* .063; Fisher exact (2-sided) *P* .14.

and 4 in at least 7 subjects (greater than 40%) who received the liposome bupivacaine mixture (GEE *P* .008) (Fig. 4). Among subjects who received bupivacaine HCl alone, no weakness was reported within 24 hours after injection. In contrast, subjects who received the liposome bupivacaine mixture experienced weakness, which subsided by the end of the fourth treatment day (GEE *P* .03). Assessment of subjects' sensorimotor block and ability to adduct and abduct the fingers (intrinsic hand muscles) by the research staff just before finger manipulation at 48 hours revealed that no subject who received bupivacaine HCl alone had residual sensory or motor block. In contrast, all subjects who received liposome bupivacaine had some degree of both sensory and motor

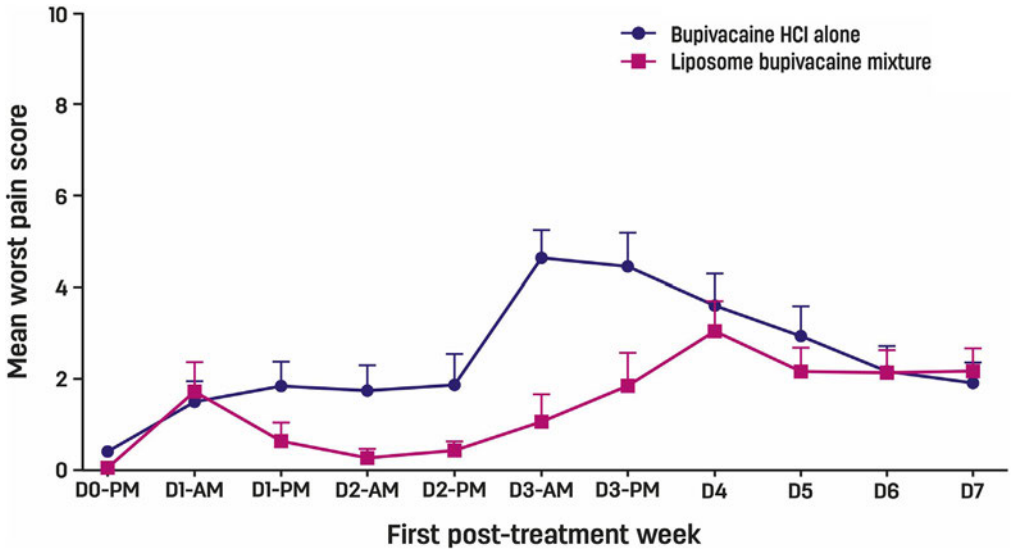

Figure 3. Mean worst (NRS) pain scores with 95% confidence interval from discharge after phase 2 through first posttreatment week in 32 subjects undergoing forearm blocks for Dupuytren contracture release (GEE *P* .01 over the first 3 days).

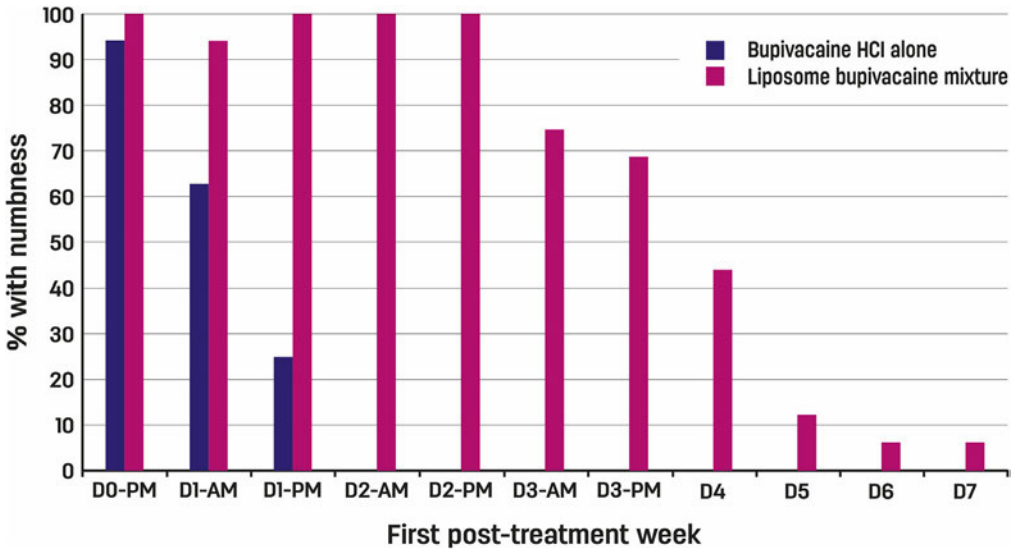

Figure 4. Sensory block (numbness) from discharge after phase 2 through first posttreatment week in 32 subjects undergoing forearm blocks for Dupuytren contracture release. Among subjects who received bupivacaine HCl alone, the percentage who reported numbness decreased rapidly within the first 48 hours; in contrast, numbness appeared to persist through days 3 and 4 in at least 40% of subjects who received the liposome bupivacaine mixture (GEE *P* .008).

block and weakness in adduction abduction of the fingers ($P <$ .001). This indicated that the duration of the blockade with liposome bupivacaine mixture exceeded that of bupivacaine HCl alone. Prolonged numbness and subjectively reported weakness did not appear to affect hand function, as assessed by subjects' ability to use a polystyrene foam cup throughout the first post treatment week.

Skin tears frequently occur during finger manipulation for Dupuytren contracture release. In this study, almost all subjects had skin tears that were successfully treated by bandaging the hand after the cords were released. No subject reported symptoms consistent with local anesthetic systemic toxicity, including bradycardia, hypotension, arrhythmia, and seizure. There were no differences in occurrence of reported side effects between treat ment arms (relative risk for at least one side effect 1.33; 95% confidence interval, 0.35–5.03) (Table 2).

Discussion

The addition of liposome bupivacaine 1.33% to bupivacaine HCl 0.5% in median and ulnar nerve blocks prolonged the duration of sensory block and analgesia compared with bupivacaine HCl alone in subjects with Dupuytren contracture release with injections of CCH. Injections of collagenase resulted in inflammatory response, ecchy mosis, and swelling of the treated hand in all research subjects, requiring adequate analgesia. As opposed to subjects treated with the liposome bupivacaine mixture, nearly all in the active compar ator group required lidocaine injections for additional analgesia. Overall, pain intensity was relatively low in both groups, probably because all subjects received multimodal analgesia. Regardless, worst pain in the first 72 hours was lower among subjects who received the liposome bupivacaine mixture than in those who received bupivacaine HCl alone. This extended analgesic effect likely

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Table 2
Frequency of Side Effects Among 32 subjects Undergoing Forearm Blocks of Median and Ulnar Nerves for Dupuytren Contracture Release

Side Effect	Mixture of 5 mL Liposome Bupivacaine 1.3% Plus 2.5 mL Bupivacaine HCl 0.5% (per Median and Ulnar Nerve) (n 16)	7.5 mL Bupivacaine HCl 0.5% per Median and Ulnar Nerve) (n 16)
None	12 (75)	13 (81)
Unique subjects with side effects, n	4 (25)	3 (19)
Total side effects, n*	6 (38)	5 (31)
Specific side effect*		
Bleeding wound	1 (6)	0
Dizziness	0	1 (6)
Headache	2 (12)	1 (6)
Itching of skin	1 (6)	1 (6)
Nausea	0	1 (6)
Sleepless night	2† (12)	1 (6)

Data are shown as n (%). Percentages of specific side effects are based on n 16 in each group. Relative risk for at least one side effect 1.33 (95% confidence interval, 0.35 5.03).

* Percentages for total number of side effects and specific side effects do not sum to 100% because some subjects reported more than one side effect.

† Sleepless nights in the same subject on 2 separate dates.

resulted from the prolongation of sensory blockade by sustained release of free bupivacaine released from liposomes and was longer by approximately threefold compared with bupivacaine HCl alone (3.8 vs 1.1 days, respectively; $P < .001$). The prolonged sensory block did not prevent any subject from using a polystyrene foam cup.

Liposome bupivacaine is a novel formulation of bupivacaine HCl, and no dosing recommendations or dose–response studies in the distal peripheral nerves of the upper extremity were available from the literature. Nonetheless, limited dosing information is available from several studies in which the drug was used for the brachial plexus block and the larger nerve blocks. For instance, injection of 133 mg (10 mL) of liposome bupivacaine resulted in successful femoral block.[12] Moreover, 5 mL of 0.25% bupivacaine HCl imme diately followed by 10 mL of liposome bupivacaine 133 mg in the interscalene brachial plexus block prolonged sensory block and analgesia with the same volume (15 mL) of bupivacaine 0.25%.[6] Because the median and ulnar nerve surface areas to be blocked in the current study are 30% to 50% that of the femoral nerve, we empirically chose to mix 5 mL of liposome bupivacaine and 2.5 mL of bupivacaine HCl 0.5%.[13,14] We relied on the relative difference in anatomical size between the femoral nerve and the smaller pe ripheral nerves to approximate the dosing for the current study. Although this may not be an ideal dose or mixture, there was no guidance in the literature suggesting a different dose. Bupivacaine HCl 0.5% was added to liposome bupivacaine to speed the onset of anesthesia for the CCH injection procedure because the liposome bupivacaine suspension contains only 3% of free drug available for immediate blockade, which would not be adequate to result in fast onset of the blockade.

The liposome bupivacaine group received a larger total dose of bupivacaine: 79 mg of bupivacaine HCl (a combination of 66.5 mg bupivacaine HCl in liposome bupivacaine 5 mL plus 12.5 mg bupivacaine HCl) compared with the bupivacaine HCl–alone group (37.5 mg bupivacaine HCl). Nonetheless, the actual dose of free bupivacaine available for nerve blockade after injection was larger in the bupivacaine HCl–alone group than in the liposome bupiva caine group (37.5 versus 14.5 mg, respectively). The liposome bupivacaine suspension contains only 3% of free bupivacaine (66.5 mg × 3% ~ 2 mg + 12.5 mg 14.5 mg), and pharmacokinetic studies showed that free bupivacaine is gradually released from the lipo somes over 72 hours or more, which is distinctly different from an injection of bupivacaine HCl alone, in which the entire dose (7.5 mL bupivacaine 0.5% 37.5 mg) is immediately available for nerve blockade. The duration of blockade by free bupivacaine from the liposome bupivacaine suspension is limited because only a small amount of free drug is quickly absorbed. Hence, any duration of analgesia beyond 36 hours is likely caused by the extended release of free bupivacaine from liposome bupivacaine, rather than a function of the larger total mass of bupivacaine HCl in the liposome bupivacaine group.[11,15,16]

A limitation of this study is that surgical dressings made motor assessments difficult. Nonetheless, analgesic benefit, rather than hand function, was the primary purpose of the study. We therefore opted to ask the subjects whether they could use a polystyrene foam cup, and about their perception of numbness or weakness in the surgical hand. Indirect assessment over the phone of their ability to hold a polystyrene foam cup and their perception of numbness and/or weakness of the surgical hand suggested that any motor block was minor or nonexistent. This could be because liposome bupivacaine releases small amounts of bupivacaine HCl over 72 hours after injection, which may be adequate for autonomic and sensory blockade but not for motor blockade. The study did not include plasma pharmacokinetic determination; however, no sub jects had signs or symptoms of systemic toxicity or electrocardio gram abnormality suggestive of local anesthetic systemic toxicity.

Another limitation of the study is that a comparison with local infiltration was not performed, although it is a common practice among hand surgeons. Nerve block and infiltration models require different methods of drug administration. We believe that a more direct comparison of the efficacy of liposome bupivacaine versus bupivacaine HCl was examined by using the nerve block model alone. Nonetheless, because local infiltration is a common practice among hand surgeons, future studies that include an infiltration arm of the trial should be conducted.

The addition of liposome bupivacaine prolonged sensory block for both phases of Dupuytren contracture release and improved pain scores in the first posttreatment week. Future studies of the efficacy of liposome bupivacaine in more extensive and recon structive hand surgeries are indicated. Studies should also be conducted to determine the dose–response and best anatomical sites of application of liposome bupivacaine that optimize nerve exposure to small amounts of active drug released in a sustained fashion from the liposomes, detailed examination of the hand function after forearm blocks with liposome bupivacaine, and cost efficacy of the treatments.

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EXHIBIT C

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Research Article Open Access

Analgesia after Hallux Valgus Osteotomy Posterior Tibial and Deep Peroneal Nerve Ankle Blocks with Bupivacaine Liposome Injectable Suspension+Bupivacaine HCl *vs.* Bupivacaine HCl *vs.* General Anesthesia Alone: A Randomized Clinical Trial

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Abstract

Background: Many patients having hallux valgus osteotomy report sustained postoperative pain. We hypothesized that the addition of bupivacaine liposome injectable suspension to bupivacaine HCl in ankle blocks decreases postoperative pain and opioid consumption compared to bupivacaine HCl alone or to general anesthesia (GA).

Methods: After EC and FAGG approval, 40 subjects scheduled for corrective osteotomy received ultrasound-guided blocks of the posterior tibial and deep peroneal (ankle) nerves with a mixture of liposome bupivacaine 1.33% and bupivacaine HCl 0.5% (5 ml and 2.5 ml, respectively, per nerve; n=12), bupivacaine HCl 0.5% alone (7.5 ml per nerve; n=14), or GA alone (n=14). All received multimodal postsurgical analgesia and opioids for breakthrough pain. Pain scores and opioid consumption were assessed through the first postoperative week.

Results: The blocked groups had lower pain scores (GEE p=0.016) and shorter PACU stay than the GA group. Mean total opioid consumption exhibited stepwise differences from 9.6 MME (mg morphine equivalents) in the liposome bupivacaine mixture group, 26.8 MME in the bupivacaine HCl alone group, to 60.4 MME in the GA group. Compared to the bupivacaine HCl alone and GA groups, a greater proportion of subjects who received the liposome bupivacaine mixture were able to ambulate through Day 4 (GEE p=0.007). There were no neurological deficits.

Conclusion: Addition of liposome bupivacaine in ultrasound-guided ankle blocks prolongs analgesia and decreases opioid consumption compared to bupivacaine HCl alone and GA, and improves ambulation after hallux valgus surgery.

Keywords: Bupivacaine liposome injectable suspension; Hallux valgus; Ankle block; Analgesia

Introduction

Corrective osteotomy for hallux valgus repair is a painful procedure that is commonly done on an outpatient basis [1] Peripheral nerve blocks can be used in the perioperative care of patients undergoing this type of surgery to improve postoperative pain [2]. However, the duration of action of the currently available local anesthetics is often insufficient for effective postoperative pain management, even with adjuvants such as clonidine or dexamethasone [3,4]. Moreover, some researchers suggest that when the blocks wear off before resolution of postoperative pain, patients may experience return of severe pain [5]. Efforts to improve postoperative pain management have led to increases in opioid prescriptions, [6]. However, opioid usage can lead to tolerance, worse treatment outcomes, addiction and overdose deaths [7]. An extended release formulation of bupivacaine liposome injectable suspension (EXPAREL®, Pacira Pharmaceuticals, Parsippany, NJ, USA) has been approved for infiltration [8]. If its perineural application in ankle blocks is effective, addition of liposome bupivacaine to bupivacaine HCl could extend the duration of sensory blocks and analgesia [9,10]. In one study, femoral nerve blocks with liposome bupivacaine modestly improved analgesia compared to placebo in patients having knee arthroplasty [11]. In another study of brachial plexus blocks, addition of bupivacaine liposome suspension extended the duration of analgesia in patients having shoulder surgery [12]. In April 2018, the US FDA approved liposome bupivacaine for use in the interscalene block. However, no study to date has evaluated the efficacy of liposome bupivacaine in the distal peripheral nerves of the lower extremity as compared to the active comparator, bupivacaine HCl alone.

This randomized clinical trial compares level of postoperative pain relief conferred by ultrasound guided ankle blocks administered with a liposome bupivacaine mixture to that conferred by 0.5% bupivacaine HCl alone or to GA in patients having corrective osteotomy for hallux valgus. We hypothesized that the liposome bupivacaine mixture prolongs analgesia and decreases opioid consumption as compared to bupivacaine HCl alone or to GA in the setting of postoperative

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multimodal analgesia. We further hypothesized that the three groups would differ in their ability to ambulate.

Level of Evidence

Level II, therapeutic study.

Materials and Methods

This double blind randomized controlled trial was approved by the Ethics Committee, by the federal agency for medicines and health products and registered with clinicaltrials.gov. Eligible subjects were scheduled for unilateral hallux valgus repair by corrective (Scarf) osteotomy. Inclusion criteria were male or female, 18 65 years of age, American Society of Anesthesiologists (ASA) physical status I III, able to understand the purpose and risks of the study, and able to discern sensory function to cold, pinprick, and light touch. Subjects were excluded if they were pregnant, were scheduled for bilateral repairs or had a previous hallux valgus repair on the ipsilateral side. Exclusion criteria also comprised a history of allergy to local anesthetics or pain medications given for our standard institutional multimodal postoperative pain management (Diclofenac, acetaminophen, tramadol), had a suspected or known recent history (<3 months) of drug or alcohol abuse, infection at the planned block site, body weight <40 kg (88 pounds) or body mass index >44 kg/m^2, any chronic neuromuscular deficit affecting the peripheral nerves or muscles of the surgical extremity, or any chronic condition or psychiatric disorder that would interfere with neurological or other study assessments.

Consenting subjects were randomized in a computer generated 1:1:1 ratio to receive (A) Ultrasound guided specific ankle blocks of the posterior tibial and deep peroneal nerves with a liposome bupivacaine mixture consisting of bupivacaine liposome injectable suspension 1.3% (5 ml) and 0.5% bupivacaine HCl (2.5 ml) per nerve (7.5 ml per nerve; 15 ml total), (B) Ultrasound guided specific ankle blocks of the posterior tibial and deep peroneal nerves with 0.5% bupivacaine HCl alone (7.5 ml per nerve; 15 ml total), or (C) GA. In addition, all subjects received the standard regimen for postoperative pain control with Diclofenac 75 mg BID and paracetamol/acetaminophen 1 g q6 h. Transmucosal tramadol 50 mg (q6 h, PRN) was used for breakthrough pain.

Anesthesiologists who performed the nerve blocks were not blinded to drug treatment arm but did not participate in subject assessments. Surgeons and research personnel were blinded to treatment arm as blocks were performed in a separate block room outside of the operating theater. To maintain blinding, all subjects received dressings as they would for regional anesthesia procedures before entering the OR. Block onset and offset times were recorded by personnel who did not participate in the postoperative assessments. Subjects were not told their allocated treatment. Subjects remained at the Surgery Day Care Center until reaching a Modified Post Anesthesia Discharge Scoring System (MPADSS) rating of at least 9 [13].

Nerve blocks (posterior tibial and deep peroneal)

All blocks were administered under ultrasound guidance. Distribution of the injectate was deemed adequate when it encircled the tibial and deep peroneal nerves. A confirmatory ultrasound image of injectate distribution was obtained by the unblinded investigator for each nerve, and maintained in a sealed envelope and placed in a locked cabinet.

Prior to performing the blocks, all subjects had an intravenous line and standard ASA monitors placed. The blocks were performed in a 'block room' at least 30 min prior to surgery with the subjects in supine. The skin was disinfected with an alcohol solution of chlorhexidine. A subcutaneous infiltration with 5 ml of 0.25% bupivacaine was used to block the cutaneous nerve branches on the medial aspect of the distal foot.

A high frequency (12 MHz) linear transducer was placed between the medial malleolus and the Achilles tendon, and the posterior tibial nerve was identified in the vicinity of the posterior tibial artery. Subjects assigned to the liposome bupivacaine mixture received an ultrasound guided perineural injection of 7.5 ml of the mixture, while subjects assigned to the bupivacaine HCl alone group received an ultrasound guided perineural injection of 7.5 ml of bupivacaine HCl 0.5%. All blocks were performed using a Uniplex Nanoline 25 G 35 mm stimulating needle (Pajunk® GmbH Medizintechnologie, Geisingen, Germany). The posterior tibial nerve was identified underneath the medial retinaculum and in the vicinity of the tibial artery. The deep peroneal nerve was located between the two malleoli and lateral to the anterior tibial artery. For each nerve, subjects assigned to the liposome bupivacaine mixture received an ultrasound guided perineural injection of 7.5 ml of the mixture, while subjects assigned to the bupivacaine HCl alone group received an ultrasound guided perineural injection of 7.5 ml of bupivacaine HCl. Thus, for the two nerves, a total of 15 ml was administered in the blocked groups. The described ultrasound guided ankle block is the standard protocol in our center for hallux valgus correction with first metatarsal osteotomy. It provides good surgical anesthesia and postoperative analgesia without foot drop that is seen in sciatic nerve popliteal nerve block. Preoperatively, all subjects received ketorolac 30 mg and acetaminophen/paracetamol 1 g prior to the start of surgery. Block failure was defined as unsatisfactory analgesia as reported by the subject in the first 2 h postoperatively or a need to convert to GA for surgery.

General anesthesia

Subjects received a standardized general anesthesia. Induction was performed with propofol Target Controlled Infusion (TCI) 4.0 6.0 mcg/ml^{-1} and fentanyl 3 mcg/kg^{-1}. Subjects subsequently received intravenous ondansetron 4 mg, ketorolac 30 mg, and acetaminophen 1 g. After induction, a laryngeal mask was placed and anesthesia was maintained with N20 50% and propofol TCI 3.0 4.0 mcg/ml^{-1}.

Postoperative management and assessments

All subjects were discharged with a standardized postoperative pain treatment consisting of acetaminophen/paracetamol 1 g q6h and diclofenac 75 mg BID. Transmucosal tramadol 50 mg (q6h PRN) was used for breakthrough pain. No other postoperative opioids were allowed. Upon injection, sensory block was measured by cold, pinprick, and light touch testing. Sensory block (rated as complete sensation; paresthesia, light touch; anesthesia, no sensation) was assessed at baseline (0 min) and every 5 min up to 30 min, at 1 and 2 h, and at hospital discharge. Worst pain (Modified BRIEF) was reported as a Numeric Rating Scale (NRS) score ranging from 0 (no pain) to 10 (most extreme pain) [14]. The NRS was recorded pre and post block. Blinded research staff collected NRS *via* phone interviews at 24 h (D1 am), 36 h (D1 pm), 48 h (D2 am), 60 h (D2 pm), 72 h (D3 am), 84 h (D3 pm), and at D4, D5, D6 and D7. Discharge readiness from the surgery day care center was evaluated by the MPADSS, an objective

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assessment for managing fair and safe discharge from the hospital setting which considers vital signs, ambulation, nausea and vomiting, pain, and surgical bleeding. Patients who achieve a score of 9 or more are considered ready for discharge [13]. Subjects were assessed through follow up phone calls at 24 h (D1 am), 36 h (D1 pm), 48 h (D2 am), 60 h (D2 pm), 72 h (D3 am), 84 h (D3 pm), and on D4, D5, D6 and D7 to query their use of opioids, presence/absence of numbness and/or weakness in the surgical foot, their ability to walk 10 steps and presence of any side effects through the first postoperative week.

Side effects, recorded through Day 7, included nausea, vomiting, fever, constipation, severe itching of the skin, dizziness, sleepless nights, excessive sweating, urinary retention, headache, and heart palpitations. Persistent neurological deficit was defined as any presence of sensory deficit or paresthesia in the distributions of the posterior tibial and deep peroneal nerves at the subject's follow up visit with the surgeon approximately 29 days post surgery. Any occurrence of neurological deficit was followed until the deficit resolved.

Statistical analysis

Sample size estimations are based on the primary outcome, here, the Numeric Rating Scale (NRS) an 11 point metric that has good reliability and validity. The ~30% difference clinically important to detect was deemed to be 3 points on the NRS as suggested by Farrar et al. [15] for chronic pain patients, by Krebs et al. [16] for primary care patients motivated to see a physician because of pain, and more recently by Leigheb et al. [17] for acute pain patients seen in an emergency department. As described in that narrative and in the manuscript, 14 subjects per group were required to test differences in NRS important to detect (Δ) 3.0 and standard deviation 2.5 at 2 sided Type I error (α) 0.05 and power (1 β). Continuous variables are presented as mean ± standard deviation; discrete (nominal, ordinal) variables as n (%). Efficacy analyses followed intent to treat principles. To address the primary research hypothesis, worst pain and ambulation were analyzed by generalized estimating equations (GEE) to examine group differences over time. GEE is flexible with respect to type of outcome variable (including possibly skewed continuous distributions and ordinal measures) and to unequally spaced observations over time. For instance, worst pain and satisfaction with pain control are reported at discharge (D0 pm), at D1 am and pm, D2 am and pm, D3 am and pm, and then on D4, D5, D6 and D7. In the GEE analyses, a conservative unstructured correlation structure was used in order not to assume the relative magnitude of correlation between any two pairs of observations (though GEE is robust against choosing an incorrect correlation structure). Link function was 'identity' for these continuous outcome measures.

The only postoperative opioid allowed as per protocol was tramadol. Postoperative tramadol consumption was converted into milligram morphine equivalents (MME) to provide a standard unit. According to Korff et al. 10 mg tramadol PO equals 1 mg morphine PO [18]. The data was submitted to a 1 way ANOVA. Comparison of pairwise group differences were Bonferroni corrected. Duration of sensory block was defined as time to reach complete sensation or full strength, respectively, and was compared by Student t test between the two treatment groups that received nerve blocks; $p<0.05$ deemed statistically significant. The GA group was not included in these analyses.

Tests of differences among groups for reported side effects were not planned as the number of each side effect was anticipated to be small, and subjects could report more than one side effect. Instead, the relative risk (with 95% confidence interval, CI) for at least one side effect through Day 7 was reported. The Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY: IBM Corp.) was used for the analyses. p values < 0.05 were deemed to be beyond chance.

Results

Forty two subjects (14/group) were randomly assigned. Upon surgical examination in the OR, two subjects, both randomly assigned to the general anesthesia group, required more extensive procedures than the corrective osteotomies specified for this trial; no further data were collected for these subjects (Figure 1). The groups did not differ in their sociodemographic characteristics or clinical features (Table 1). All subjects successfully completed the protocol in their assigned groups; there were no block failures.

Ankle blocks significantly reduced pain scores through the first postoperative week (GEE p=0.016) (Figure 2). Mean total postoperative opioid consumption was highest in the GA alone group (60.4 MME), slightly higher than the overall median in the bupivacaine HCl alone group (26.8 MME), and lowest in the liposome bupivacaine mixture group (9.6 MME) ($p<0.001$). Bonferroni corrected p values for these stepwise differences revealed GA alone compared to bupivacaine HCl alone (p=0.048) and to liposome bupivacaine mixture ($p<0.001$); bupivacaine HCl alone compared to liposome bupivacaine mixture (p=0.152) (Figure 3). Figure 4 shows the mean daily opioid consumption between the three groups. Subjects who received an ankle block were discharged from the PACU approximately 30 min after surgery, whereas patients who received GA alone stayed significantly longer in the PACU (31.4 ± 13.9 *vs.* 69.3 ± 32.5 min, respectively, p=0.002). Duration of sensory block was longer in the liposome bupivacaine mixture group than in the bupivacaine alone group (93.8 ± 41.6 versus 62.2 ± 19.6 h, p=0.03). A greater proportion of subjects who received the liposome bupivacaine mixture were able to ambulate daily (walk 10 steps) through Day 4 compared to the bupivacaine HCl alone and GA groups (GEE p=0.007). No subject reported symptoms consistent with local anesthetic systemic toxicity (LAST), including bradycardia, hypotension, arrhythmia, seizure. Side effects occurred with low but similar relative risk with no differences among the groups (Table 2). There were no persistent neurological deficits.

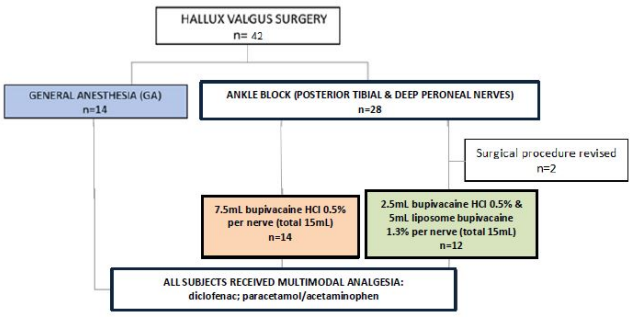

Figure 1: CONSORT diagram.

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Variables	Liposome bupivacaine mixture (n=12)	Bupivacaine HCl alone (n=14)	General anesthesia (GA) (n=14)
Gender (M:F)	01:11	00:14	00:14
Mean Age in y (SD)	47.1 ± 14.0	46.5 ± 13.7	44.7 ± 11.4
BMean MI in kg/m^2 (SD)	25.1 ± 2.8	23.8 ± 3.5	22.5 ± 2.4
Race, n (%)			
American Indian/Alaska na ive	0	0	0
Asian	0	0	0
Black/African American	0	1 (7)	0
Native Hawaiian/Pacific islander	0	0	0
White	12 (100)	13 (93)	14 (100)
Other	0	0	0
ASA physical status, n (%)			
I	9 (75)	10 (71)	8 (57)
II	3 (25)	4 (29)	6 (43)
III	0	0	0
Surgical side (R:L)	07:05	05:09	03:10
Functionality of surgical foot[a], n (%)			
Slight restrictions only	4 (33)	2 (14)	4 (31)
Normal	8 (67)	12 (86)	9 (69)
Numeric Rating Scale (NRS)(0-10)[b] (SD)			
At rest	0.2 (0.6)	0.8 (1.5)	0.8 (1.7)
During movement	4.2 (2.7)	3.0 (2.4)	4.5 (2.6)
[a]Functionality missing on 1 subject (GA group), despite of pain, patients did not report limitations in their normal activity			
[b]Pre-block NRS rest and movement scores missing on 1 subject (GA group)			

Table 1: Sociodemographic characteristics and pre block clinical features of 40 subjects undergoing ankle blocks or general anesthesia for corrective osteotomy for hallux valgus.

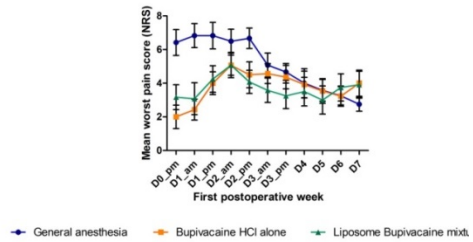

Figure 2: Mean worst pain (Modified BRIEF Q1) (NRS scores with standard errors) from discharge through the first postoperative week in 40 subjects undergoing corrective osteotomy for hallux valgus (overall p=0.016).

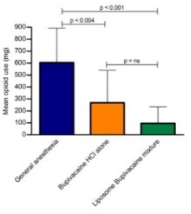

Figure 3: Mean total opioid use (mg morphine equivalent with standard deviations) through the first postoperative week in 40 subjects undergoing corrective osteotomy for hallux valgus (poverall F<0.001). p values for pairwise comparisons Bonferroni corrected.

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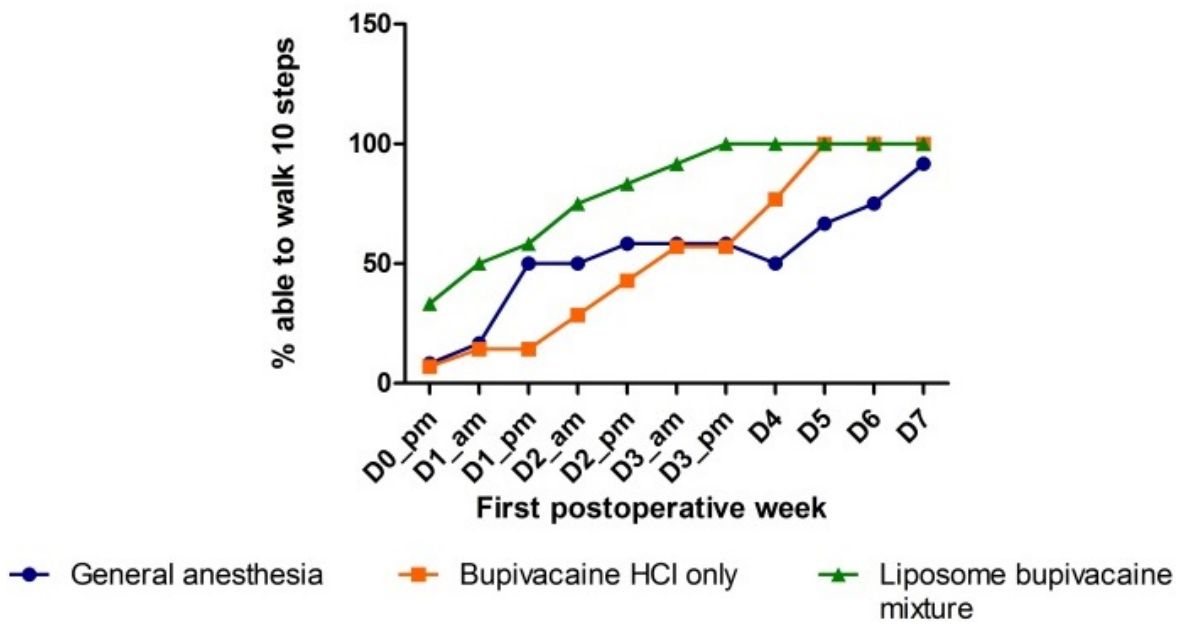

Figure 4: Percent able to ambulate (walk 10 steps) in 40 subjects undergoing corrective osteotomy for hallux valgus in the first postoperative week (overall p=0.007).

Adverse event[a]	**Liposome bupivacaine mixture (n=12)**	**Bupivacaine HCl alone (n=14)**	**General anesthesia (GA) (n=14)**
Unique subjects reporting adverse events[b]	3	8	6
No. of adverse events	5	16	18
Adverse events			
Nausea	2	3	10
Vomiting	2	-	2
Fever	-	-	-
Constipation	-	1	-
Severe itching of the skin	-	3	-
Dizziness	1	7	3
Sweating	-	-	1
Urinary retention	-	-	1
Headache	-	1	1
Heart palpitations	-	1	-
[a]Total percentages do not sum to 100% as some subjects reported >1 adverse event			
[b]Relative risk for at least 1 adverse event			
Liposome bupivacaine mixture and bupivacaine HCl alone: 2.3 (95% CI 0.8, 6.7)			
Liposome bupivacaine mixture and GA: 0.6 (95% CI 0.2, 1.8)			
Bupivacaine HCl alone and GA: 1.3 (95% CI 0.6, 2.8)			

Table 2: Adverse events reported by 40 subjects undergoing corrective osteotomy for hallux valgus with ankle blocks or general anesthesia in the time interval from PACU discharge to postoperative Day 7.

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Discussion

To our knowledge, this study is the first to examine the analgesic effect of liposome bupivacaine administered perineurally to block the distal peripheral nerves of the lower extremity. The addition of liposome bupivacaine to bupivacaine HCl 0.5% reduced pain and mean opioid consumption after hallux valgus correction with first metatarsal osteotomy. Duration of sensory block was longer in subjects who received the liposome bupivacaine mixture without hindering ambulation; these subjects were better able to ambulate than subjects who received bupivacaine HCl alone or GA.

Deaths from prescription opioids have more than quadrupled since 1999 [19]. Prescription opioids in the postoperative setting of orthopedic surgery have been identified as a major factor in the current opioid pandemic [20]. Subjects given the liposome bupivacaine mixture used far less opioids as rescue medication for their postoperative pain than subjects given GA, and even when compared to subjects given bupivacaine HCl alone. Thus methods of conferring effective postsurgical analgesia by extended nerve blocks may help to reduce or minimize the need for opioid prescriptions in the management of postoperative pain.

Liposome bupivacaine is a novel formulation of bupivacaine, approved for infiltration but not for peripheral nerve blocks. Consequently, no dosing recommendations were available in the literature to guide dose and mixture selection for the current trial. Nonetheless, some dosing information is available from several studies in which the drug has been used to block the larger nerves and the brachial plexus. For instance, injection of 133 mg (10 ml) of liposome bupivacaine resulted in successful femoral block [11]. In another study, 5 ml of 0.25% bupivacaine HCl immediately followed by 10 ml of liposome bupivacaine 133 mg in interscalene brachial plexus block prolonged sensory block and analgesia of the same (15 ml) volume of bupivacaine HCl 0.25% [12]. The only other studies available to us where liposome bupivacaine was studied for forefoot surgery used wound infiltration in patients having forefoot surgery, whereas ankle block were accomplished with and lidocaine 2% or a mixture of lidocaine 1% and marcaine 0.5% [21,22].

Since the nerve surface area of the posterior tibial and deep peroneal nerves is 50% that of the femoral nerve, we empirically chose to mix 5 ml of liposome bupivacaine and 2.5% of bupivacaine HCl 0.5%. Thus the relative difference in anatomical size between the femoral nerve and the smaller peripheral nerves was used to calculate the dosing for the current study.

Bupivacaine 0.5% was added to liposome bupivacaine to accomplish rapid onset of anesthesia for the procedure. The liposome bupivacaine suspension contains only 3% of the free drug available for immediate blockade, which would not be adequate for fast onset of the block. Finally, the liposome bupivacaine mixture group received a larger total dose of bupivacaine: 79 mg of bupivacaine HCl (combination of 66.5 mg bupivacaine HCl in liposome bupivacaine 5 ml + 12.5 mg bupivacaine HCl) compared to the bupivacaine HCl alone group (37.5 mg bupivacaine HCl). However, the duration of free bupivacaine HCl is limited as the drug is quickly absorbed from the site of injection and, therefore, unavailable for re uptake by NaCl channels as the block wears off. Therefore, any duration of analgesia beyond 36 hours is likely due to the extended release of bupivacaine HCl from liposome bupivacaine, rather than a function of the larger total mass of bupivacaine HCL in the liposome bupivacaine group.

A potential risk of exparel in ankle block is that patients may lack of protective sensation due to the prolonged nerve blockade. No adverse events were reported. As per protocol all subjects received verbal and written instructions on how to keep the limb protected until complete recuperation of sensory block.

Even more the subjects all had postoperative bandages at the level of the forefoot for one week which impaired proprioception as well and served as a protection for potential harmful stimuli in the forefoot.

A limitation of this study is its relatively small sample size. As described, sample size was estimated on the NRS pain scores and assumed a commonly used minimum difference important to detect of 3 NRS points. Likewise, we anticipated a large standard deviation that reflects wide variability in duration of peripheral nerve blocks [23]. Even larger variability in block duration could be anticipated with the liposomal formulation due to the slow and extended release of its active substance, bupivacaine HCl, over a longer postoperative interval (72 hours) [23]. Another limitation of this study is that use of tramadol for breakthrough pain and postoperative pain scores were not treated in an integrated analysis [24]. However, such analyses would likely require the accuracy afforded by IV PCA delivered opioids to subjects admitted as inpatients for longer than 24 h. The information of consumption of tramadol tablets was collected by phone interview without an actual pill count; therefore a potential reporting bias on opioid consumption cannot be excluded.

Conclusion

In conclusion, addition of liposome bupivacaine in ultrasound guided ankle blocks prolongs analgesia and decreases opioid consumption compared to bupivacaine HCl alone and GA and improves ambulation after hallux valgus surgery.

Acknowledgement

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Conflict of Interest

This study was supported by a research grant from Pacira Pharmaceuticals, Inc. (Parsippany, NJ, USA). Dr. Hadzic serves as a consultant to Pacira Pharmaceuticals, Inc. and has received consulting honoraria, educational and research grants.

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